Paul

93482

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Ganapathy Krishnan Examiner #: 79271 Date: 5/7/03
Art Unit: 1623 Phone Number 30 5-4537 Serial Number: 09/787764
Mail Box and Bldg/Room Location: 8D08 Results Format Preferred (circle): PAPER DISK E-MAIL
8B19

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Please see bib sheet.

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Need structure search of formula I in claim 22, and the method in claim 22.

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MAY - 7 2003
(STIC)

POINT OF CONTACT:
PAUL SCHULWITZ
TECHNICAL INFO. SPECIALIST
CM1 6B06 TEL. (703) 305-1954

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher:	NA Sequence (#)		STN	632.06
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)	1	Questel/Orbit	
Date Searcher Picked Up:	5/8	Bibliographic	Dr.Link	
Date Completed:	5/8	Litigation	Lexis/Nexis	
Searcher Prep & Review Time:	30	Fulltext	Sequence Systems	
Clerical Prep Time:		Patent Family	WWW/Internet	
Online Time:	74	Other	Other (specify)	

PTO-1590 (8-01)

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                TYPE CB1"+OLD/CT
L5              STR
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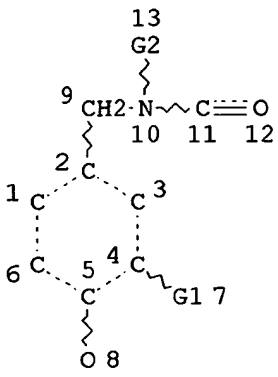

Ak @22

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VAR G2=H/22
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CONNECT IS E3  RC AT  11
CONNECT IS E1  RC AT  14
CONNECT IS E1  RC AT  16
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CONNECT IS E2  RC AT  20
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CONNECT IS E1  RC AT  22
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT  18
GGCAT   IS UNS  AT  21
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS X7 C  AT  18
ECOUNT  IS M6 C  AT  21

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L6          2379 SEA FILE=REGISTRY SSS FUL L5
L10         1246 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (CB1 OR CB 1) AND CANNABIN?
L11           29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND (L1 OR L10)

=> d ibib abs hitstr l11 1-29

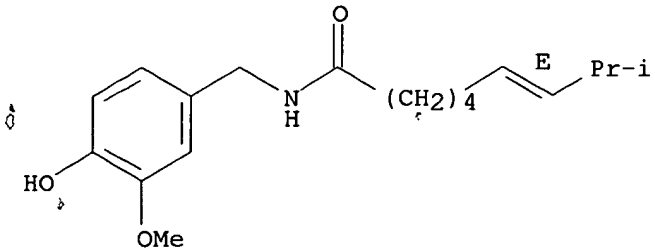
L11  ANSWER 1 OF 29  HCAPLUS  COPYRIGHT 2003 ACS
```

ACCESSION NUMBER: 2002:932629 HCAPLUS
DOCUMENT NUMBER: 138:181073
TITLE: Estrogen stimulates arachidonoylethanolamide release from human endothelial cells and platelet activation
AUTHOR(S): Maccarrone, Mauro; Bari, Monica; Battista, Natalia; Finazzi-Agro, Alessandro
CORPORATE SOURCE: Department of Experimental Medicine and Biochemical Sciences, University of Rome Tor Vergata, Rome, I-00133, Italy
SOURCE: Blood (2002), 100(12), 4040-4048
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogen replacement therapy has been assocd. with redn. of cardiovascular events in postmenopausal women, though the mechanism for this benefit remains unclear. At physiol. concns. estrogen activates the anandamide membrane transporter of human endothelial cells and leads to rapid elevation of calcium (apparent within 5 min) and release of nitric oxide (within 15 min). These effects are mediated by estrogen binding to a surface receptor, which shows an apparent dissocn. const. (Kd) of 9.4.+-.1.4 nM, a max. binding (Bmax) of 356.+-.12 fmol .times. mg protein-1, and an apparent mol. mass of approx. 60 kDa. The authors also show that estrogen binding to surface receptors leads to stimulation of the anandamide-synthesizing enzyme phospholipase D and to inhibition of the anandamide-hydrolyzing enzyme fatty acid amide hydrolase, the latter effect mediated by 15-lipoxygenase activity. Because the endothelial transporter is shown to move anandamide across the cell membranes bidirectionally, taken together these data suggest that the physiol. activity of estrogen is to stimulate the release, rather than the uptake, of anandamide from endothelial cells. Moreover, the authors show that anandamide released from estrogen-stimulated endothelial cells, unlike estrogen itself, inhibits the secretion of serotonin from ADP-stimulated platelets. Therefore, it is suggested that the peripheral actions of anandamide could be part of the mol. events responsible for the beneficial effects of estrogen.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (estrogen stimulates arachidonoylethanolamide release from human endothelial cells and platelet activation in relation to modulation by various compds.)
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

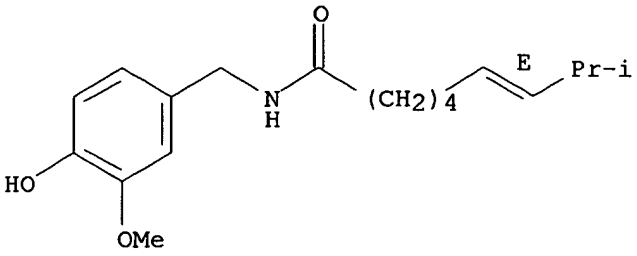
L11 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:741775 HCAPLUS
DOCUMENT NUMBER: 138:117804
TITLE: Pharmacological separation of **cannabinoid** sensitive receptors on hippocampal excitatory and inhibitory fibers
AUTHOR(S): Hajos, N.; Freund, T. F.
CORPORATE SOURCE: Institute of Experimental Medicine, Department of Functional Neuroanatomy, Hungarian Academy of Sciences, Budapest, H-1450, Hung.
SOURCE: Neuropharmacology (2002), 43(4), 503-510
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors' earlier studies demonstrated that in the hippocampus, **cannabinoids** suppress inhibitory synaptic transmission via **CB1 cannabinoid** receptors, whereas a novel **cannabinoid**-sensitive receptor modulates excitatory synapses. The novel receptor does not correspond to CB2, since this receptor type is not expressed in the brain. Recent binding expts. revealed that the synthetic **cannabinoid** WIN 55,212-2 binds with lower affinity to brain membranes of **CB1** receptor-knockout mice indicating that pharmacol. differences exist between these two types of **cannabinoid** receptors in the hippocampus. To analyze this difference in detail, the authors first detd. the EC50 values of WIN 55,212-2 for excitatory and inhibitory transmission in rat hippocampal slices using whole-cell patch-clamp recordings. The estd. EC50 value for inhibitory postsynaptic currents (IPSC) evoked by elec. stimulation in CA1 pyramidal cells was 0.24 .mu.M, whereas for excitatory postsynaptic currents (EPSC) it was 2.01 .mu.M, resp. The **cannabinoid** antagonist, AM251, blocked the WIN 55,212-2-induced inhibition of evoked IPSCs, but not of EPSCs, providing evidence for its selectivity for **CB1**. The authors then tested the hypothesis of whether the **cannabinoid** effect on hippocampal excitatory neurotransmission is mediated via receptors with an affinity for vanilloid ligands. Co-application of the vanilloid receptor antagonist capsazepine (10 .mu.M) with **cannabinoids** (WIN55,212-2 or CP55,940) prevented the redn. of EPSCs, but not of IPSCs. The amplitude of evoked EPSCs was also suppressed by superfusion of the vanilloid receptor agonist capsaicin (10 .mu.M), an effect which could also be antagonized by capsazepine. In contrast, capsaicin did not change the amplitude of evoked IPSCs. These results demonstrate that WIN 55,212-2 is an order of magnitude more potent in reducing GABAergic currents via **CB1** than in inhibiting glutamatergic transmission via the new CB receptor. The sensitivity of the new CB receptor (and EPSCs) to vanilloid ligands, but not to the **cannabinoid** antagonist AM251, represents another pharmacol. tool to distinguish the two receptors, since **CB1** (and its effect on IPSCs) is not modulated by vanilloids, but is antagonized by AM251.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. sepn. of **cannabinoid** sensitive receptors on rat hippocampal excitatory and inhibitory fibers)
RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:674650 HCAPLUS
DOCUMENT NUMBER: 138:235364
TITLE: Characterization of the anandamide induced depolarization of guinea-pig isolated vagus nerve
AUTHOR(S): Kagaya, Manabu; Lamb, Jasmine; Robbins, Jon; Page, Clive P.; Spina, Domenico
CORPORATE SOURCE: The Sackler Institute of Pulmonary Pharmacology, GKT School of Biomedical Science, King's College London, London, SE1 1UL, UK
SOURCE: British Journal of Pharmacology (2002), 137(1), 39-48
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1 There is considerable interest in elucidating potential endogenously derived agonists of the vanilloid receptor and the role of anandamide in this regard has received considerable attention. In the present study, we have used an electrophysiol. technique to investigate the mechanism of activation of vanilloid receptors in an isolated vagal prepn. 2 Both capsaicin and anandamide depolarized de-sheathed whole vagal nerve prepns. that was antagonized by the VR1 antagonist, capsazepine ($P<0.05$) while this response was unaltered by the **cannabinoid** (**CB1**) selective antagonist SR141716A or the CB2 selective antagonist, SR144528, thereby ruling out a role for **cannabinoid** receptors in this response. 3 The PKC activator, phorbol-12-myristate-13-acetate (PMA) augmented depolarization to both anandamide and capsaicin and this response was significantly inhibited with the PKC inhibitor, bisindolylmaleimide (BIM) ($P<0.05$). 4 The role of lipoxygenase products in the depolarization to anandamide was investigated in the presence of the lipoxygenase inhibitor, 5,8,11-Eicosatriynoic acid (ETI). Depolarization to anandamide and arachidonic acid was significantly inhibited in the presence of ET1 ($P<0.05$). However, in the absence of calcium depolarization to anandamide was not inhibited by ETI. 5 Using confocal microscopy we have demonstrated the presence of vanilloid receptors on both neuropeptide contg. nerves and nerves that did not stain for sensory neuropeptides. 6 These results demonstrate that anandamide evokes depolarization of guinea-pig vagus nerve, following activation of

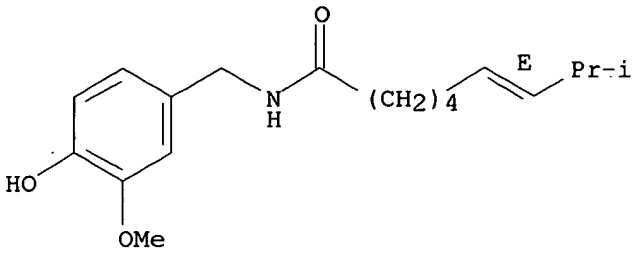
vanilloid receptors, a component of which involves the generation of lipoxygenase products. Furthermore, these receptors are distributed in both neuropeptide and non-neuropeptide contg. nerves.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(capsaicin and anandamide activation of vanilloid receptors in induction of depolarization in guinea-pig isolated vagus nerve)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:646595 HCAPLUS

DOCUMENT NUMBER: 138:198368

TITLE: Mechanisms underlying tissue selectivity of anandamide and other vanilloid receptor agonists

AUTHOR(S): Andersson, David A.; Adner, Mikael; Hogestatt, Edward D.; Zygmunt, Peter M.

CORPORATE SOURCE: Department of Clinical Pharmacology, Institute of Laboratory Medicine, Lund University Hospital, Lund University, Lund, Swed.

SOURCE: Molecular Pharmacology (2002), 62(3), 705-713
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

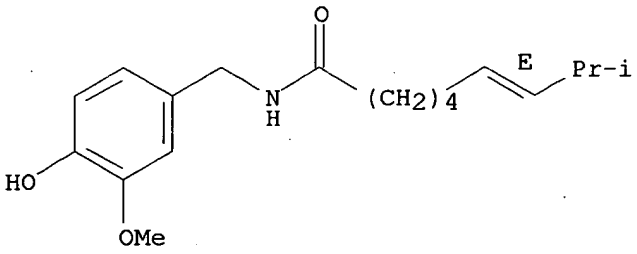
AB Anandamide acts as a full vanilloid receptor agonist in many bioassay systems, but it is a weak activator of primary afferents in the airways. To address this discrepancy, we compared the effect of different vanilloid receptor agonists in isolated airways and mesenteric arteries of guinea pig using prepns. contg. different phenotypes of the capsaicin-sensitive sensory nerve. We found that anandamide is a powerful vasodilator of mesenteric arteries but a weak constrictor of main bronchi. These effects of anandamide are mediated by vanilloid receptors on primary afferents and do not involve **cannabinoid** receptors. Anandamide also contracts isolated lung strips, an effect caused by the hydrolysis of anandamide and subsequent formation of cyclooxygenase products. Although capsaicin is equally potent in bronchi and mesenteric arteries, anandamide, resiniferatoxin, and particularly olvanil are significantly less potent in bronchi. Competition expts. with the vanilloid receptor antagonist

capsazepine did not provide evidence of vanilloid receptor heterogeneity. Arachidonoyl-5-methoxytryptamine (VDM13), an inhibitor of the anandamide membrane transporter, attenuates responses to olvanil and anandamide, but not capsaicin and resiniferatoxin, in mesenteric arteries. VDM13 did not affect responses to these agonists in bronchi, suggesting that the anandamide membrane transporter is absent in this phenotype of the sensory nerve. Computer simulations using an operational model of agonism were consistent, with differences in intrinsic efficacy and receptor content being responsible for the remaining differences in agonist potency between the tissues. This study describes differences between vanilloid receptor agonists regarding tissue selectivity and provides a conceptual framework for developing tissue-selective vanilloid receptor agonists devoid of bronchoconstrictor activity.

IT **404-86-4**, Capsaicin **58493-49-5**, Olvanil
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanisms underlying tissue selectivity of anandamide and other vanilloid receptor agonists)

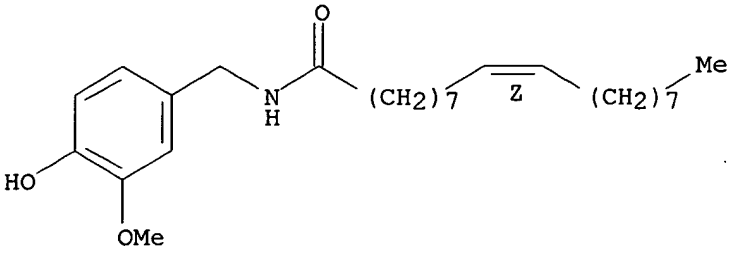
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 58493-49-5 HCAPLUS
CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2003 ACS

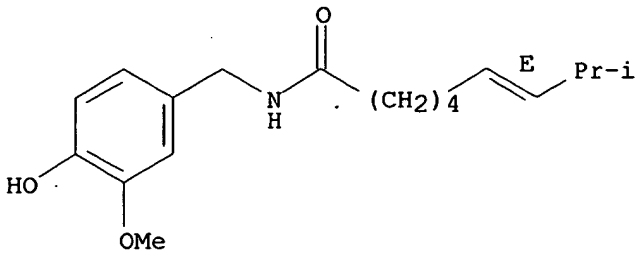
ACCESSION NUMBER: 2002:456448 HCAPLUS
DOCUMENT NUMBER: 138:130915
TITLE: The effect of **cannabinoids** on capsaicin-evoked calcitonin gene-related peptide (CGRP) release from the isolated paw skin of diabetic and non-diabetic rats
AUTHOR(S): Ellington, Heather C.; Cotter, Mary A.; Cameron, Norman E.; Ross, Ruth A.
CORPORATE SOURCE: Department of Biomedical Sciences, University of Aberdeen, Institute of Medical Sciences, Aberdeen, Foresterhill, AB25 2ZD, UK
SOURCE: Neuropharmacology (2002), 42(7), 966-975
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sensory neural dysfunction is common in patients with peripheral neuropathy, a major complication of diabetes mellitus. In animal models of inflammatory and neuropathic pain **cannabinoids** potently attenuate pain behavior, **cannabinoid** (CB) receptors located on nociceptive primary afferent neurons being important in their anti-hyperalgesic actions. A key measure of sensory neuron function is stimulus-evoked neuropeptide release. The authors investigated the effect of **cannabinoid** on capsaicin-evoked release of calcitonin gene-related peptide (CGRP) from the rat paw skin in vitro, comparing non-diabetic and streptozotocin-induced diabetic animals. Diabetes caused a greater than two-fold increase in basal and capsaicin-evoked CGRP release. The synthetic **CB1**/CB2 receptor agonist, CP55940 (100 nM), inhibited capsaicin-evoked CGRP release in both non-diabetic (30.92.+-.7.69%, P<0.05) and diabetic animals (37.82.+-.9.85%, P<0.05). The **CB1** receptor antagonist SR141716A (100 nM), but not the CB2 receptor antagonist SR144528 (100 nM), significantly attenuated the inhibitory action of CP55940. The endogenous **cannabinoid**, anandamide (100 nM) inhibited capsaicin-evoked CGRP release in non-diabetic animals (28.88.+-.7.12%, P<0.05) but neither the **CB1** nor the CB2 receptor antagonist attenuated this action of anandamide. Anandamide (100 nM) did not significantly inhibit capsaicin-evoked CGRP release from the paw skin of diabetic animals, but it did produce a small stimulation of CGRP release at high concns. (10 .mu.M). These data suggest that peripheral **CB1** receptors mediate inhibition of capsaicin-evoked neuropeptide release from the paw skin of both non-diabetic and diabetic animals. However, pathol. changes in the diabetic animals appear to preclude the non-**CB1** receptor mediated inhibitory action of the endogenous **cannabinoid**, anandamide.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of **cannabinoids** on capsaicin-evoked calcitonin gene-related peptide release from the isolated paw skin of diabetic and non-diabetic rats and receptors involved)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:435013 HCAPLUS
DOCUMENT NUMBER: 138:579
TITLE: Pharmacological characterization of the anandamide cyclooxygenase metabolite: Prostaglandin E2 ethanolamide
AUTHOR(S): Ross, Ruth A.; Craib, Susan J.; Stevenson, Lesley A.; Pertwee, Roger G.; Henderson, Andrea; Toole, John; Ellington, Heather C.
CORPORATE SOURCE: Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, AB25 2ZD, UK
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 301(3), 900-907
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anandamide can be metabolized by cyclooxygenase-2 to produce prostaglandin E2 (PGE2) ethanolamide. The purpose of this study was to investigate the pharmacol. of this novel compd. Radioligand binding expts. in membranes from human embryonic kidney cells transfected with PGE2 receptor subtypes EP1, EP2, EP3, and EP4 revealed that PGE2 ethanolamide has pKi values of 5.61.+-.0.1, 6.33.+-.0.01, 6.70.+-.0.13, and 6.29.+-.0.06, resp., compared with 8.31.+-.0.16, 9.03.+-.0.04, 9.34.+-.0.06, and 9.10.+-.0.04 for PGE2. PGE2 inhibits elec. evoked contractions of the guinea pig vas deferens (EP3 receptor-mediated), with a pEC50 value of 9.09.+-.0.06, compared with that of 7.38.+-.0.09 for PGE2 ethanolamide. In the guinea pig trachea, 100 nM PGE2 and 1 .mu.M PGE2 ethanolamide produced contractions of 51.8.+-.10.6 and 38.9.+-.5.6% (of the histamine Emax), resp. The EP1 receptor antagonist SC-51089 (10 .mu.M) prevented the contractions induced by both compds. In the presence of 10 .mu.M 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[1-oxo-3-(4-pyridinyl)propyl]hydrazide, monohydrochloride (SC-51089), PGE2 caused a concn.-related relaxation of histamine-induced contractions of this tissue (EP2 receptor-mediated), the pEC50 value being 8.29.+-.0.17 compared with that of 7.11.+-.0.18 for PGE2 ethanolamide. In the rabbit jugular vein, PGE2 induces relaxation (EP4 receptor-mediated) with a pEC50 of 9.35.+-.0.25, compared with 7.05.+-.0.4 for PGE2 ethanolamide. In dorsal root ganglion neurons in culture, 3 .mu.M PGE2 ethanolamide evoked an increase in intracellular calcium concn. in 21% of small-diam. capsaicin-sensitive neurons. The authors conclude that this compd. is

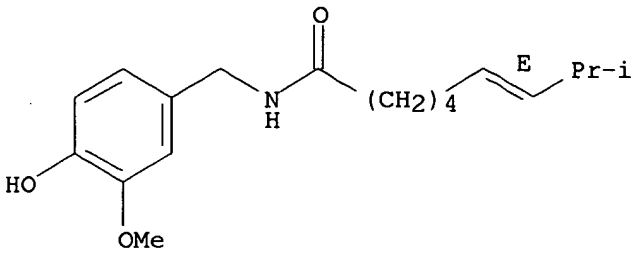
pharmacol. active, however its physiol. relevance has yet to be established.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of anandamide cyclooxygenase metabolite prostaglandin E2 ethanolamide in human and animal tissues)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:323024 HCAPLUS

DOCUMENT NUMBER: 137:245168

TITLE: Stimulation of pulmonary vagal C-fibres by anandamide in anaesthetized rats: role of vanilloid type 1 receptors

AUTHOR(S): Lin, You Shuei; Lee, Lu-Yuan

CORPORATE SOURCE: Department of Physiology, University of Kentucky, Lexington, KY, 40536, USA

SOURCE: Journal of Physiology (Cambridge, United Kingdom) (2002), 539(3), 947-955
CODEN: JPHYA7; ISSN: 0022-3751

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study was carried out to det. the effect of i.v. injection of anandamide on pulmonary C-fiber afferents and the cardiorespiratory reflexes. In anesthetized, spontaneously breathing rats, i.v. bolus injection of anandamide near the right atrium immediately elicited the pulmonary chemoreflex responses, characterized by apnea, bradycardia and hypotension. After perineural treatment of both cervical vagi with capsaicin to block the conduction of C-fibers, anandamide no longer evoked these reflex responses. In open-chest, and artificially ventilated rats, anandamide injection evoked an abrupt and intense discharge in vagal pulmonary C-fibers in a dose-dependent manner. After injection of the high dose, the fiber discharge generally started within 1 s, reached a peak in .apprx.2 s, and returned to baseline within 7 s. The stimulation of C-fibers by anandamide was completely and reversibly blocked by pretreatment with capsazepine, a competitive antagonist of the vanilloid type 1 receptor. Anandamide (0.4 mg kg-1) stimulated .apprx.93% of pulmonary C-fibers that were activated by capsaicin at a much lower dose

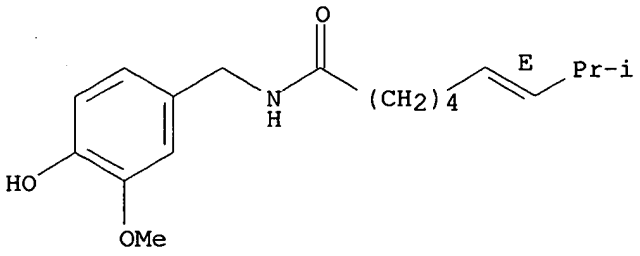
(0.6 .mu.g kg-1); the response to anandamide showed similar intensity, but had slightly longer latency and duration than that to capsaicin. In conclusion, i.v. bolus injection of anandamide evokes a consistent and distinct stimulatory effect on pulmonary C-fiber terminals, and this effect appears to be mediated through an activation of the vanilloid type 1 receptor.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(comparison with; anandamide effects on pulmonary C-fiber afferents and cardiorespiratory reflexes in anesthetized rats in relation role of vanilloid type 1 receptors and **CB1** receptors)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:323019 HCAPLUS

DOCUMENT NUMBER: 137:245167

TITLE: Characterization of vasorelaxant responses to anandamide in the rat mesenteric arterial bed

AUTHOR(S): Harris, David; McCulloch, Audrey I.; Kendall, David A.; Randall, Michael D.

CORPORATE SOURCE: School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham Medical School, Nottingham, NG7 2UH, UK

SOURCE: Journal of Physiology (Cambridge, United Kingdom) (2002), 539(3), 893-902
CODEN: JPHYA7; ISSN: 0022-3751

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The endogenous **cannabinoid** anandamide has recently been identified as a vasorelaxant but the underlying mechanisms are controversial. The vasorelaxant responses to anandamide have now been examd. in the rat mesenteric arterial bed. Anandamide caused potent vasorelaxations (pD2 = 6.24.+-.0.06; Rmax = 89.4.+-.2.2%) which were unaffected by inhibition of nitric oxide synthase with NG-nitro-L-arginine Me ester (L-NAME; 300 .mu.M). The responses were also predominantly endothelium independent and were unaffected by the **cannabinoid** **CB1** receptor antagonist SR141716A (1 .mu.M), although at higher concns. (3 and 10 .mu.M) SR141716A was inhibitory. Both 1 mM ouabain (pD2

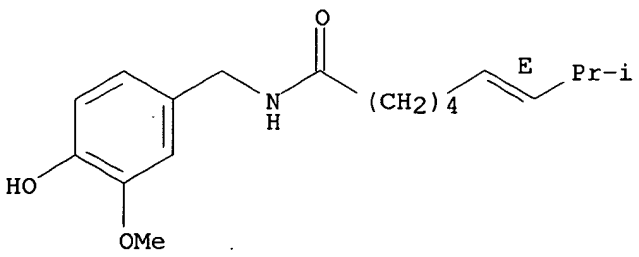
= 5.90.+-.0.07; Rmax = 50.4.+-.6.5%) and 100 .mu.M 18.alpha.-glycyrrhetinic acid (pD2 = 6.04.+-.0.14; Rmax = 40.9.+-.5.8%) opposed anandamide-induced vasorelaxation. However, the gap junction inhibitors carbenoxolone (100 .mu.M) and palmitoleic acid (50 .mu.M) did not affect vasorelaxation to anandamide. Relaxation to anandamide was significantly attenuated by both capsaicin pretreatment to deplete the sensory nerves of neurotransmitters (pD2 = 5.86.+-.0.18; Rmax = 56.3.+-.5.2%) and the vanilloid antagonist ruthenium red (10 .mu.M; pD2 = 5.64.+-.0.09; Rmax = 33.7.+-.3.9%). However, these inhibitory effects were prevented by the addnl. presence of L-NAME, when the relaxation to anandamide was unaffected (pD2 = 6.19.+-.0.07; Rmax = 81.9.+-.2.8%). The inhibitor of neuronal nitric oxide synthase, 7-nitroindazole, also prevented capsaicin from inhibiting the responses to anandamide. The results of this study point to anandamide acting via several mechanisms, which include the involvement of sensory nerves, but only in the presence of nitric oxide.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mechanisms involved in vasorelaxant responses to anandamide in rat mesenteric arterial bed)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:249802 HCAPLUS

DOCUMENT NUMBER: 137:242055

TITLE: Arvanil-induced inhibition of spasticity and persistent pain: evidence for therapeutic sites of action different from the vanilloid VR1 receptor and **cannabinoid CB1**/CB2 receptors

AUTHOR(S): Brooks, Jason W.; Pryce, Gareth; Bisogno, Tiziana; Jaggar, Sian I.; Hankey, Deborah J. R.; Brown, Peter; Bridges, Daniel; Ledent, Catherine; Bifulco, Maurizio; Rice, Andrew S. C.; Di Marzo, Vincenzo; Baker, David

CORPORATE SOURCE: Faculty of Medicine, Department of Anaesthetics, Pain Research Group, Chelsea and Westminster Hospital Campus, Imperial College, London, UK

SOURCE: European Journal of Pharmacology (2002), 439(1-3), 83-92
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of **cannabinoid** receptors causes inhibition of spasticity, in a mouse model of multiple sclerosis, and of persistent pain, in the rat formalin test. The endocannabinoid anandamide inhibits spasticity and persistent pain. It not only binds to **cannabinoid** receptors but is also a full agonist at vanilloid receptors of type 1 (VR1). We found here that vanilloid VR1 receptor agonists (capsaicin and N-N'-(3-methoxy-4-aminoethoxy-benzyl)-(4-tert-butyl-benzyl)-urea [SDZ-249-665]) exhibit a small, albeit significant, inhibition of spasticity that can be attenuated by the vanilloid VR1 receptor antagonist, capsazepine. Arvanil, a structural "hybrid" between capsaicin and anandamide, was a potent inhibitor of spasticity at doses (e.g. 0.01 mg/kg i.v.) where capsaicin and **cannabinoid CB1** receptor agonists were ineffective. The anti-spastic effect of arvanil was unchanged in **cannabinoid CB1** receptor gene-deficient mice or in wild-type mice in the presence of both **cannabinoid** and vanilloid receptor antagonists. Likewise, arvanil (0.1-0.25 mg/kg) exhibited a potent analgesic effect in the formalin test, which was not reversed by **cannabinoid** and vanilloid receptor antagonists. These findings suggest that activation by arvanil of sites of action different from **cannabinoid CB1**/CB2 receptors and vanilloid VR1 receptors leads to anti-spastic/analgesic effects that might be exploited therapeutically.

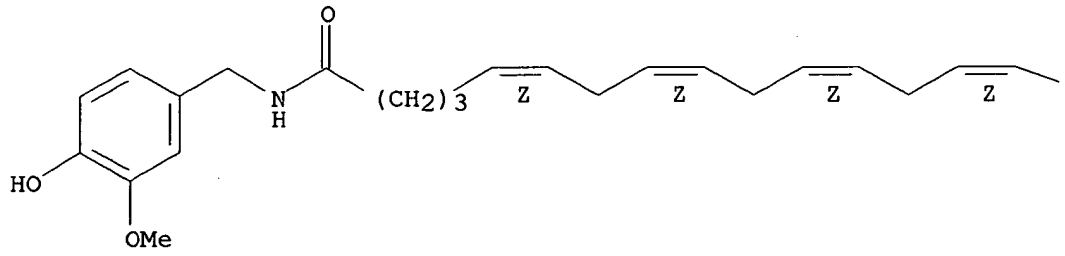
IT **128007-31-8**, Arvanil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arvanil-induced inhibition of spasticity and persistent pain)

RN 128007-31-8 HCAPLUS

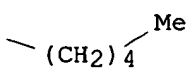
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:203609 HCAPLUS
DOCUMENT NUMBER: 137:56979
TITLE: A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid
AUTHOR(S): Di Marzo, Vincenzo; Griffin, Graeme; De Petrocellis, Luciano; Brandi, Ines; Bisogno, Tiziana; Williams, William; Grier, Mark C.; Kulasegram, Sanjitha; Mahadevan, Anu; Razdan, Raj K.; Martin, Billy R.
CORPORATE SOURCE: Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Naples, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 300(3), 984-991
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:56979

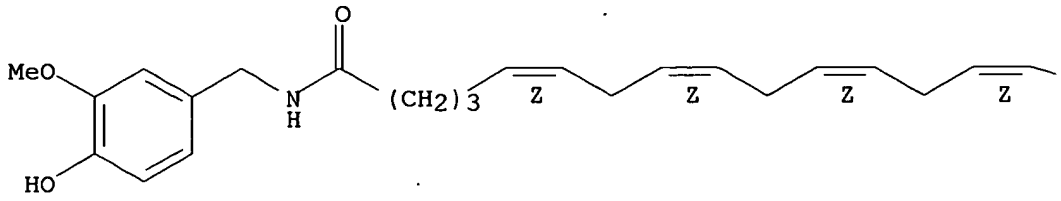
AB Arvanil, a structural "hybrid" between the endogenous **cannabinoid** **CB1** receptor ligand anandamide and capsaicin, is a potent agonist for the capsaicin receptor VR1 (vanilloid receptor type 1), inhibits the anandamide membrane transporter (AMT), and induces cannabimimetic responses in mice. Novel arvanil derivs. prepd. by N-methylation, replacement of the amide with urea and thiourea moieties, and manipulation of the vanillyl group were evaluated for their ability to bind/activate **CB1** receptors, activate VR1 receptors, inhibit the AMT and fatty acid amide hydrolase (FAAH), and produce cannabimimetic effects in mice. The compds. did not stimulate the **CB1** receptor. Methylation of the amide group decreased the activity at VR1, AMT, and FAAH. On the arom. ring, the substitution of the 3-methoxy group with a chlorine atom or the lack of the 4-hydroxy group decreased the activity on VR1 and AMT, but not the affinity for **CB1** receptors, and increased the capability to inhibit FAAH. The urea or thiourea analogs retained activity at VR1 and AMT but exhibited little affinity for **CB1** receptors. The urea analog was a potent FAAH inhibitor (IC50 = 2.0 .mu.M). A water-sol. analog of arvanil, O-2142, was as active on VR1, much less active on AMT and **CB1**, and more potent on FAAH. All compds. induced a response in the mouse "tetrad", particularly those with EC50 <10 nM on VR1. However, the most potent compd., N-N'-di-(3-chloro-4-hydroxy)benzyl-arachidonamide (O-2093, ED50 .apprx.0.04 mg/kg), did not activate VR1 or **CB1** receptors. Our findings suggest that VR1 and/or as yet uncharacterized receptors produce cannabimimetic responses in mice in vivo.

IT **322399-59-7P**, O-1861 **439079-98-8P**, O 1988
439080-02-1P, O 1987 **439080-05-4P**, O 2142
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure/activity relationship study on arvanil)

RN 322399-59-7 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, 20-bromo-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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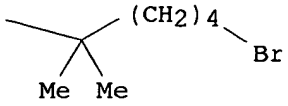
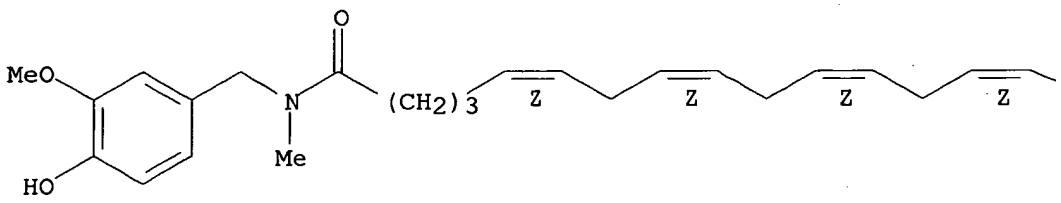


RN 439079-98-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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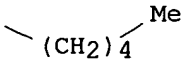
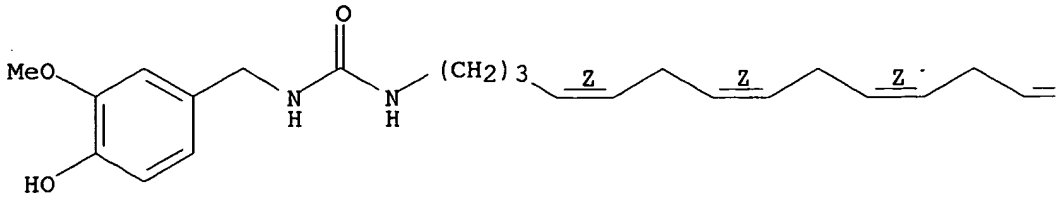


RN 439080-02-1 HCAPLUS
CN Urea, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N'-(4Z,7Z,10Z,13Z)-4,7,10,13-nonadecatetraenyl- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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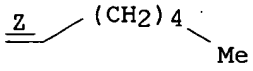
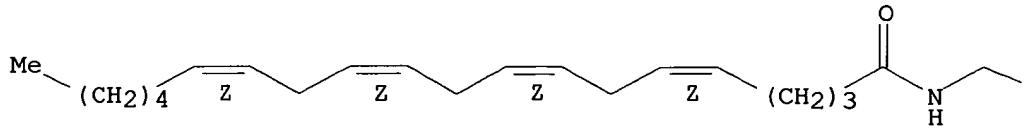


RN 439080-05-4 HCAPLUS
CN 4-Morpholinebutanoic acid, 2-methoxy-4-[[[(5Z,8Z,11Z,14Z)-1-oxo-5,8,11,14-eicosatetraenyl]amino]methyl]phenyl ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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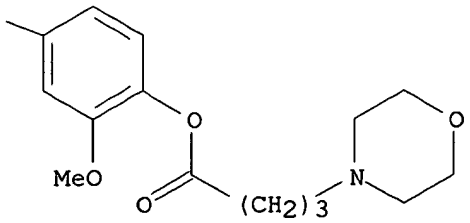
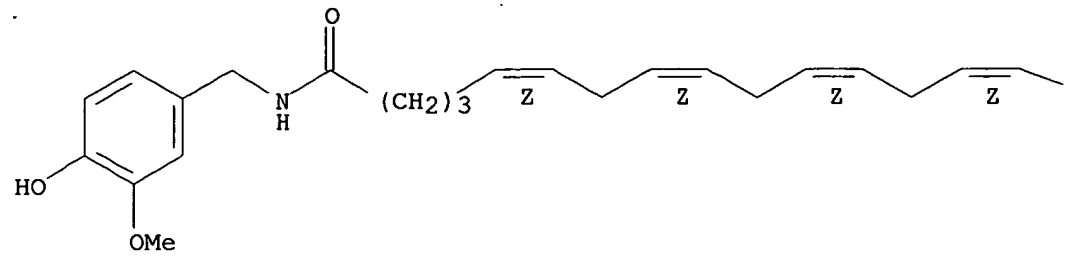


IT **128007-31-8P**, Arvanil
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(structure/activity relationship study on arvanil)
RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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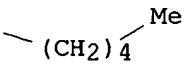
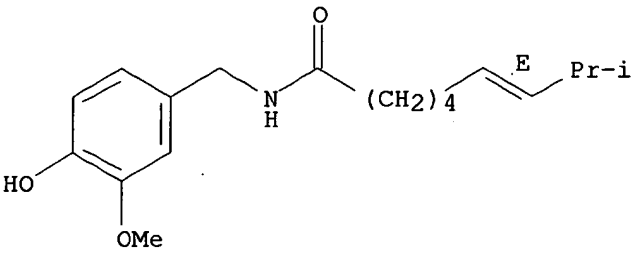


IT **404-86-4,** Capsaicin
RL: RCT (Reactant); RACT (Reactant or reagent)
(structure/activity relationship study on arvanil)
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:884754 HCAPLUS
DOCUMENT NUMBER: 136:161001
TITLE: Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic **cannabinoids**. Relative involvement of **cannabinoid** and vanilloid receptors
AUTHOR(S): Jacobsson, Stig O. P.; Wallin, Thomas; Fowler, Christopher J.
CORPORATE SOURCE: Departments of Pharmacology and Clinical Neuroscience and Odontology, Umea University, Umea, Swed.

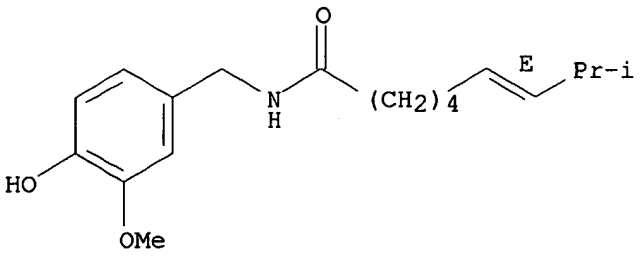
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 299(3), 951-959
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) upon rat C6 glioma cell proliferation were examd. and compared with a series of synthetic **cannabinoids** and related compds. Cells were treated with the compds. each day and cell proliferation was monitored for up to 5 days of exposure. AEA time- and concn.-dependently inhibited C6 cell proliferation. After 4 days of treatment, AEA and 2-AG inhibited C6 cell proliferation with similar potencies (IC50 values of 1.6 and 1.8 .mu.M, resp.), whereas palmitoylethanolamide showed no significant antiproliferative effects at concns. up to 10 .mu.M. The antiproliferative effects of both AEA and 2-AG were blocked completely by a combination of antagonists at **cannabinoid** receptors (SR141716A and SR144528 or AM251 and AM630) and vanilloid receptors (capsazepine) as well as by .alpha.-tocopherol (0.1 and 10 .mu.M), and reduced by calpeptin (10 .mu.M) and fumonisin B1 (10 .mu.M), but not by L-cycloserine (1 and 100 .mu.M). CP 55,940, JW015, olvanil, and arachidonoyl-serotonin were all found to affect C6 glioma cell proliferation (IC50 values of 5.6, 3.2, 5.5, and 1.6 .mu.M, resp.), but the inhibition could not be blocked by **cannabinoid** + vanilloid receptor antagonists. It is concluded that the antiproliferative effects of the endocannabinoids upon C6 cells are brought about by a mechanism involving combined activation of both vanilloid receptors and to a lesser extent **cannabinoid** receptors, and leading to oxidative stress and calpain activation. However, there is at present no obvious universal mechanism whereby plant-derived, synthetic, and endogenous **cannabinoids** affect cell viability and proliferation.

IT **404-86-4**, Capsaicin **58493-49-5**, Olvanil
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of the inhibition of rat C6 glioma cell proliferation by endogenous and synthetic **cannabinoids**)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

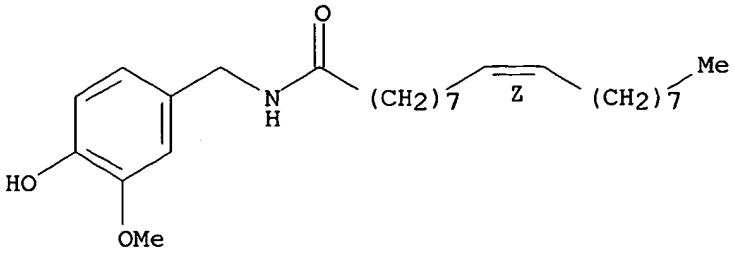
Double bond geometry as shown.



RN 58493-49-5 HCAPLUS

CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:855426 HCAPLUS
DOCUMENT NUMBER: 136:177704
TITLE: Anandamide and methanandamide induce both vanilloid VR1- and **cannabinoid CB1** receptor-mediated changes in heart rate and blood pressure in anaesthetized rats
AUTHOR(S): Malinowska, Barbara; Kwolek, Grzegorz; Goethert, Manfred
CORPORATE SOURCE: Zaklad Fizjologii Doswiadczalnej, Akademia Medyczna w Bialymstoku, Bialystok, 15-230, Pol.
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2001), 364(6), 562-569
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In anesthetized rats activation of vanilloid receptors on sensory vagal nerves elicits rapid bradycardia and hypotension (Bezold-Jarisch reflex). Recent in vitro expts. revealed that the endogenous **cannabinoid** ligand anandamide acts as an agonist at the vanilloid VR1 receptors. The present study was aimed at examg. whether vanilloid VR1 receptors are involved in the cardiovascular effects of anandamide in the anesthetized rat. I.v. injection of anandamide, its stable analog methanandamide and the vanilloid receptor agonist capsaicin produced a dose-dependent immediate and short-lasting decrease in heart rate and blood pressure with the following rank order of potencies: capsaicin > methanandamide > anandamide. This bradycardia was dose-dependently diminished by the selective vanilloid receptor antagonist capsazepine (0.3-3 .mu.mol/kg) and the nonselective inhibitor of these receptors, ruthenium red (1-10 .mu.mol/kg). Both antagonists reduced or tended to reduce the hypotension stimulated by the agonists. Following this bradycardia and hypotension (presumably evoked by the Bezold-Jarisch reflex; phase I), capsaicin, anandamide and methanandamide led to a brief vasopressor effect (phase II). Subsequently both anandamides, but not capsaicin, induced a more prolonged decrease in blood pressure (phase III). Capsazepine and ruthenium red (at doses up to 3 .mu.mol/kg and 10 .mu.mol/kg, resp.) failed to affect these changes in blood pressure. The **cannabinoid**

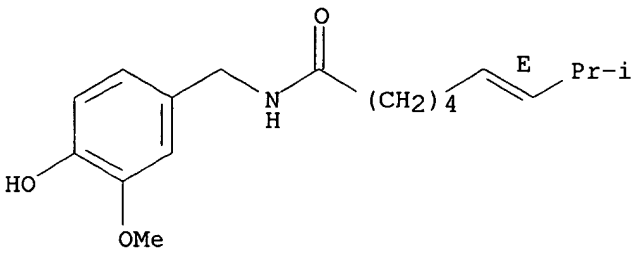
CB1 receptor antagonist SR 141716 at 3 .mu.mol/kg abolished the prolonged decrease in blood pressure (phase III) induced by anandamide and methanandamide, but had no effect on the reflex bradycardia and hypotension (phase I) and on the subsequent vasopressor effect (phase II) evoked by capsaicin, anandamide and methanandamide. In conclusion, the endogenous **cannabinoid** receptor agonist anandamide and its stable analog methanandamide induce reflex bradycardia and hypotension (phase I) by activating the vanilloid VR1 receptor. Whereas the mechanism underlying the brief vasopressor effect (phase II) is unknown, the prolonged hypotension (phase III) results from stimulation of the **cannabinoid CB1** receptor.

IT **404-86-4**, Capsaicin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(anandamide and methanandamide induce both vanilloid VR1- and **cannabinoid CB1** receptor-mediated changes in heart rate and blood pressure in anesthetized rats)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:789791 HCAPLUS

DOCUMENT NUMBER: 136:95834

TITLE: Anandamide induces cardiovascular and respiratory reflexes via vasosensory nerves in the anaesthetized rat

AUTHOR(S): Smith, Paula J. W.; McQueen, Daniel S.

CORPORATE SOURCE: Department of Neuroscience, University of Edinburgh Medical School, Edinburgh, EH8 9JZ, UK

SOURCE: British Journal of Pharmacology (2001), 134(3), 655-663
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1 We tested the hypothesis that sensory nerves innervating blood vessels play a role in the local and systemic regulation of the cardiovascular and respiratory (CVR) systems. We measured CVR reflexes evoked by administration of anandamide (86-863 nmoles) and capsaicin (0.3-10 nmoles) into the hindlimb vasculature of anesthetized rats. 2 Anandamide and capsaicin each caused a rapid dose-dependent reflex fall in blood pressure

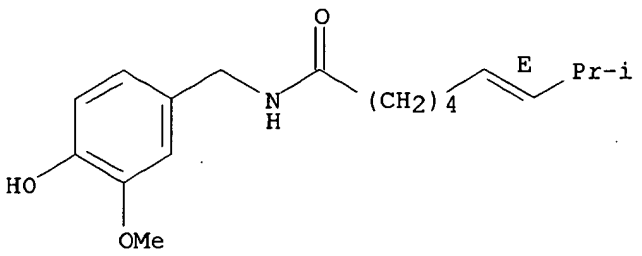
and an increase in ventilation when injected intra-arterially into the hindlimb. 3 Action of both agonists at the vanilloid receptor (VR1) on perivascular sensory nerves was investigated using capsazepine (1 mg kg-1 i.a.) a competitive VR1 antagonist, ruthenium red (1 mg kg-1 i.a.), a non-competitive antagonist at VR1, or a desensitizing dose of capsaicin (200 nmoles i.a.). The **cannabinoid** receptor antagonist SR141716 (1 mg kg-1 i.a.) was used to det. agonist activity at the **CB1** receptor. 4 Capsazepine, ruthenium red, or acute VR1 desensitization by capsaicin-pretreatment, markedly attenuated the reflex CVR responses evoked by anandamide and capsaicin ($P < 0.05$; paired Student's t-test). Blockade of **CB1** had no significant effect on the responses to anandamide. 5 Local sectioning of the femoral and sciatic nerves attenuated CVR responses to anandamide and capsaicin ($P < 0.05$). Vagotomy or carotid sinus sectioning had no significant effect on anandamide- or capsaicin-induced responses. 6 These data demonstrate that both the endogenous **cannabinoid**, anandamide, and the vanilloid, capsaicin, evoke CVR reflexes when injected intra-arterially into the rat hindlimb. These responses appear to be mediated reflexly via VR1 located on sensory nerve endings within the hindlimb vasculature.

IT **404-86-4**, Capsaicin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(anandamide induces cardiovascular and respiratory reflexes via vasosensory nerves in the anesthetized rat)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:661252 HCAPLUS

DOCUMENT NUMBER: 135:205570

TITLE: Modulators of the endocannabinoid uptake and of the vanilloid receptors

INVENTOR(S): Baker, David; Pryce, Gareth; De Marzo, Vincenzo; Bisogno, Tiziana; De Petrocellis, Luciano

PATENT ASSIGNEE(S): University College London, UK

SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064212	A1	20010907	WO 2001-GB858	20010228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

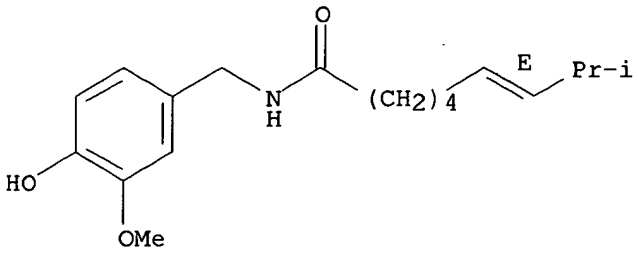
PRIORITY APPLN. INFO.: GB 2000-4895 A 20000301
GB 2000-27989 A 20001116

AB A method of treatment is described. The method comprises administering to a subject suffering from a muscular disorder a modulator of endocannabinoid and in such an amt. to treat said muscular disorder.

IT **404-86-4**, Capsaicin **104899-01-6**, Linvanil
128007-31-8, Arvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulators of endocannabinoid uptake and of vanilloid receptors to treat muscular disorders in relation to lack of effect on **CB1 cannabinoid** receptors)

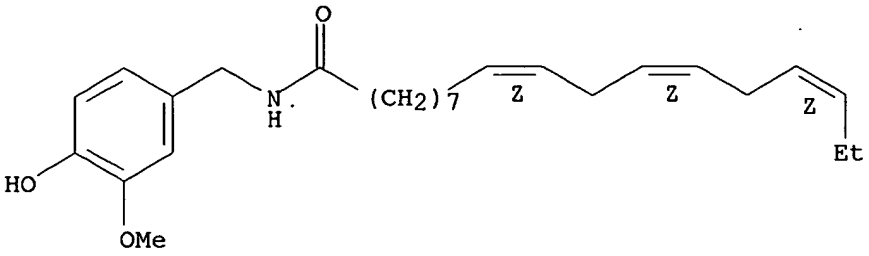
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 104899-01-6 HCAPLUS
CN 9,12,15-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

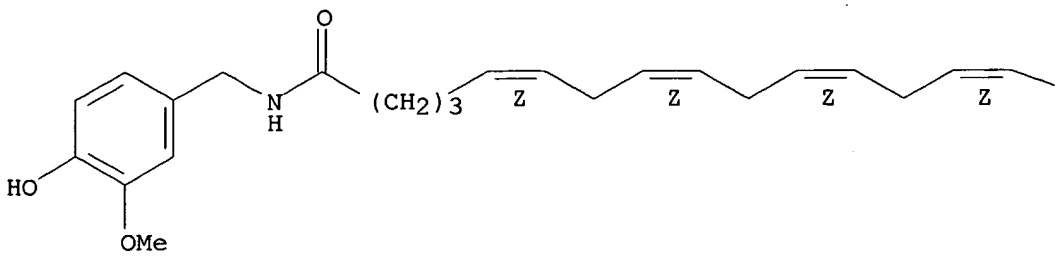
Double bond geometry as shown.



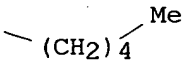
RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

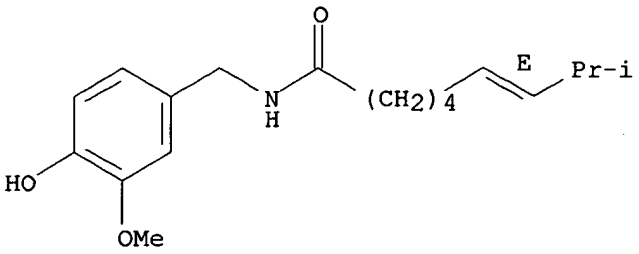
L11 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:575542 HCAPLUS
DOCUMENT NUMBER: 135:366583
TITLE: **Cannabinoid** activation of recombinant and endogenous vanilloid receptors
AUTHOR(S): Ralevic, V.; Kendall, D. A.; Jerman, J. C.; Middlemiss, D. N.; Smart, D.
CORPORATE SOURCE: School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham Medical School, Nottingham, NG7 2UH, UK
SOURCE: European Journal of Pharmacology (2001), 424(3), 211-219
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of three structurally related **cannabinoids** on human and rat recombinant vanilloid VR1 receptors expressed in human embryonic kidney (HEK293) cells and at endogenous vanilloid receptors in the rat isolated mesenteric arterial bed were studied. In the recombinant cells, all three were full agonists, causing concn.-dependent increases in [Ca2+]i (FLIPR), with a rank order of potency relative to the vanilloids capsaicin and olvanil, of olvanil .gtoreq.capsaicin >AM404 ((allZ)-N-(4-hydroxyphenyl)-5,8,11,14-eicosatetraenamide)>anandamide>metha nandamide. These responses were inhibited by the vanilloid VR1 receptor antagonist, capsazepine. In the mesenteric arterial bed, vasorelaxation was evoked by these ligands with a similar order of potency. The AM404-induced vasorelaxation was virtually abolished by capsaicin pretreatment. AM404 inhibition of capsaicin-sensitive sensory neurotransmission was blocked by ruthenium red, but not by **cannabinoid CB1** and CB2 receptor antagonists. AM404 had no effect on relaxations to calcitonin gene-related peptide. These data demonstrate that the vasorelaxant and sensory neuromodulator properties of AM404 in the rat isolated mesenteric arterial bed are mediated by vanilloid VR1 receptors.

IT **404-86-4**, Capsaicin **58493-49-5**, Olvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**cannabinoid** activation of recombinant and endogenous vanilloid receptors)

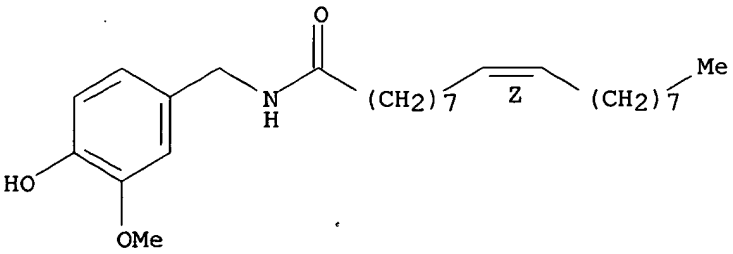
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 58493-49-5 HCAPLUS
CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

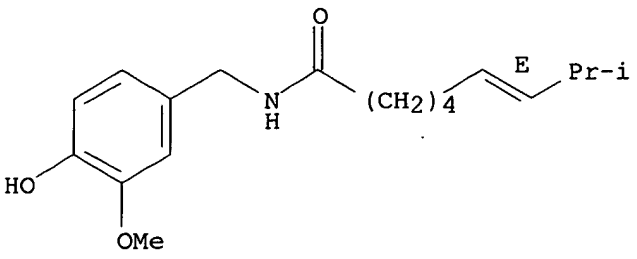
L11 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:483835 HCAPLUS
DOCUMENT NUMBER: 136:79578
TITLE: Interactions between .DELTA.9-THC and capsaicin on isolated lamb bladder detrusor
AUTHOR(S): Bartocci, C.; Evandri, M. G.; Tucci, P.; Bolle, P.
CORPORATE SOURCE: School of Pharmacy, Department of Pharmacology and Physiology, University of Rome "La Sapienza", Rome, 00185, Italy
SOURCE: Farmaco (2001), 56(5-6-7), 349-351
CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous work on isolated lamb detrusor demonstrated that capsaicin generally produces a relaxation of the tissue; this relaxation seems to be mediated by CGRP. Endogenous **cannabinoids**, such as anandamide, produce some of their actions by stimulating VR1 receptors and this seems to cause the release of peptides, e.g. CGRP. This work investigated whether a **cannabinoid**, .DELTA.9-tetrahydrocannabinol (.DELTA.-9THC), was able to interfere with the response of the isolated lamb detrusor to capsaicin. .DELTA.9-THC, at concns. 1.6.times.10-7-1.3.times.10-6 M, had no activity on this tissue. Instead, following .DELTA.9-THC, most of the samples responded to capsaicin with a contraction that was abolished by atropine (9.0 .times. 10-7M). It has been reported that **cannabinoids** can inhibit the release of CGRP by stimulation of **CB1** and CB2 **cannabinoid** receptors. .DELTA.9-THC could act by stimulating these receptors and thus inhibiting CGRP release and vesical relaxation. Removal of the muscle-relaxant component could favor the contractile component, usually not active.

IT **404-86-4**, Capsaicin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(.DELTA.9-THC and capsaicin interactions on bladder detrusor muscle)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

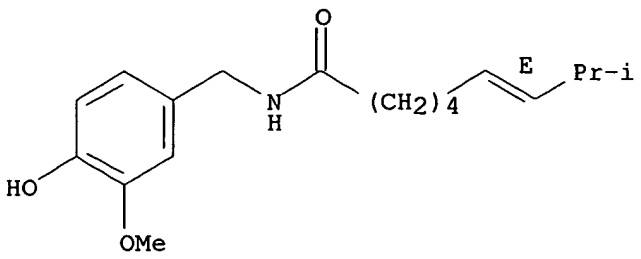
L11 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:428173 HCAPLUS
DOCUMENT NUMBER: 135:236320
TITLE: Hypolocomotor effects in rats of capsaicin and two long chain capsaicin homologues
AUTHOR(S): Di Marzo, V.; Lastres-Becker, I.; Bisogno, T.; De Petrocellis, L.; Milone, A.; Davis, J. B.; Fernandez-Ruiz, J. J.
CORPORATE SOURCE: Endocannabinoid Research Group, C.N.R., Istituto per la Chimica di Molecole di Interesse Biologico, Naples, Arco Felice, 80072, Italy
SOURCE: European Journal of Pharmacology (2001), 420(2/3), 123-131
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Capsaicin and its analog N-arachidonoyl-vanillyl-amine (arvanil) are agonists of vanilloid VR1 receptors, and suppress spontaneous activity in mice through an unknown mechanism. Here, we tested in rats the effect on motor behavior of: (1) capsaicin; (2) N-linoleoyl-vanillyl-amine (livanil) and N-.alpha.-linolenoyl-vanillyl-amine (linvanil), which, unlike arvanil, have very little affinity for **cannabinoid CB1** receptors; and (3) the endocannabinoid anandamide (N-arachidonoyl-ethanolamine), which is a full agonist at both **cannabinoid CB1** and vanilloid VR1 receptors. All compds., administered i.p., dose-dependently (0.1-10 mg/kg) inhibited ambulation and stereotypic behavior and increased inactivity in the open field test. The rank of potency obsd. in vivo (livanil>capsaicin>linvanil>anandamide) bore little resemblance with the relative potencies in a functional assay for rat vanilloid VR1 receptors (livanil=linvanil>capsaicin>anandamide) and even less with the relative affinities in rat **CB1** receptor binding assays (anandamide>livanil>linvanil>capsaicin). The vanilloid VR1 receptor antagonist capsazepine (10 mg/kg, i.p.) blocked the effect of capsaicin but not of livanil or anandamide, whereas the **CB1** receptor antagonist (N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide.HCl) (SR141716A, 3 mg/kg, i.p.) antagonized the actions of the **CB1** receptor agonist .DELTA.9-tetrahydrocannabinol, but not of livanil, anandamide or capsaicin. Anandamide occluded the effects of livanil on locomotion, possibly suggestive of a common mechanism of action for the two compds. Finally, stimulation with capsaicin of cells expressing rat vanilloid VR1 receptors led to anandamide formation. These data suggest that motor behavior can be suppressed by the activation of: (1) vanilloid receptors, possibly via the intermediacy of anandamide; or (2) capsazepine- and SR141716A-insensitive sites of action for anandamide, livanil and linvanil, possibly the same that were previously suggested to mediate arvanil hypokinetic effects in mice.

IT **404-86-4**, Capsaicin **16729-47-8**, Livanil
104899-01-6, Linvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(hypolocomotor effects in rats of capsaicin and two long chain capsaicin homologs)

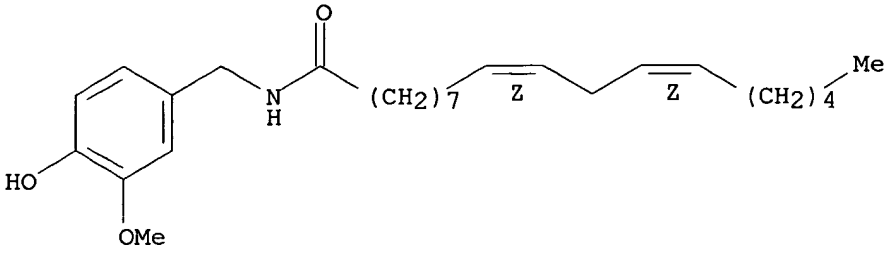
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



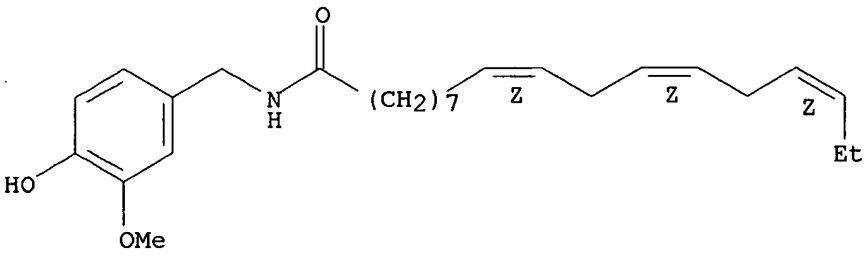
RN 16729-47-8 HCAPLUS
CN 9,12-Octadecadienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z)-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 104899-01-6 HCAPLUS
CN 9,12,15-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:315474 HCAPLUS
DOCUMENT NUMBER: 135:132113
TITLE: **Cannabinoid** inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed

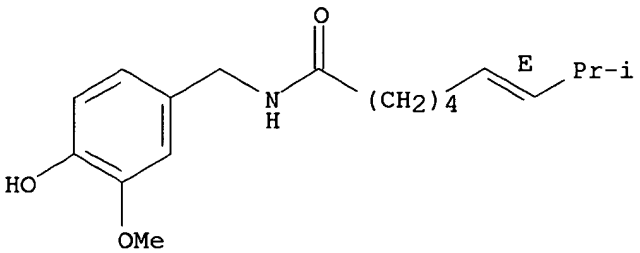
AUTHOR(S): Ralevic, V.; Kendall, D. A.
CORPORATE SOURCE: School of Biomedical Sciences, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK
SOURCE: European Journal of Pharmacology (2001), 418(1,2), 117-125
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study investigated whether **cannabinoids** can modulate neurotransmission mediated by capsaicin-sensitive sensory nerves in the rat isolated mesenteric arterial bed. Sensory neurogenic vasorelaxation mediated by elec. field stimulation was concn.-dependently attenuated by HU210 (0.1-3 .mu.M), a **cannabinoid** receptor agonist (from 62.+-.8.3% to 6.+-.2.1% at 3 .mu.M HU210). HU210 had no effect on relaxation to exogenous calcitonin gene-related peptide, indicating a prejunctional action. The action of HU210 (1 .mu.M) was not affected by LY320135 (1 .mu.M) or SR144528 (1 .mu.M), **cannabinoid CB1** and CB2 receptor antagonists, resp. SR141716A (0.01-1 .mu.M), a **cannabinoid CB1** receptor antagonist, concn.-dependently augmented vasorelaxation to elec. field stimulation, but had no effect on responses to calcitonin gene-related peptide and capsaicin, indicating a possible role of endogenous **cannabinoids** in sensory neurotransmission in rat mesenteric arteries. These data show that the **cannabinoid** receptor agonist HU210 inhibits prejunctionally sensory neurotransmission in rat mesenteric arteries and that this action is independent of **cannabinoid CB1**- or CB2-like receptors.

IT **404-86-4**, Capsaicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**cannabinoid** inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:282211 HCAPLUS

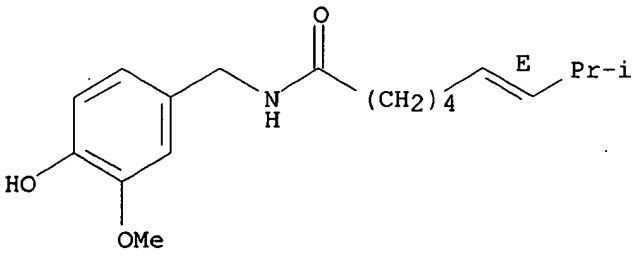
DOCUMENT NUMBER: 135:90395
TITLE: Effect of vanilloid drugs on gastrointestinal transit in mice
AUTHOR(S): Izzo, Angelo A.; Capasso, Raffaele; Pinto, Luisa; Di Carlo, Giulia; Mascolo, Nicola; Capasso, Francesco
CORPORATE SOURCE: Department of Experimental Pharmacology, University of Naples "Federico II", Naples, 80131, Italy
SOURCE: British Journal of Pharmacology (2001), 132(7), 1411-1416
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have studied the effect of capsaicin, piperine, and anandamide, drugs which activate vanilloid receptors and capsazepine, a vanilloid receptor antagonist, on upper gastrointestinal motility in mice. Piperine (0.5-20 mg kg-1 i.p.) and anandamide (0.5-20 mg kg-1 i.p.), dose-dependently delayed gastrointestinal motility, while capsaicin (up to 3 mg kg-1 i.p.) was without effect. Capsazepine (15 mg kg-1 i.p.) neither per se affected gastrointestinal motility nor did it counteract the inhibitory effect of both piperine (10 mg kg-1) and anandamide (10 mg kg-1). A per se non ED of SR141716A (0.3 mg kg-1 i.p.), a **cannabinoid CB1** receptor antagonist, counteracted the inhibitory effect of anandamide (10 mg kg-1) but not of piperine (10 mg kg-1). By contrast, the inhibitory effect of piperine (10 mg kg-1) but not of anandamide (10 mg kg-1) was strongly attenuated in capsaicin (75 mg kg-1 in total, s.c.)-treated mice. Pretreatment of mice with NG-nitro-L-arginine Me ester (25 mg kg-1 i.p.), yohimbine (1 mg kg-1, i.p.), naloxone (2 mg kg-1 i.p.), or hexamethonium (1 mg kg-1 i.p.) did not modify the inhibitory effect of both piperine (10 mg kg-1) and anandamide (10 mg kg-1). The present study indicates that the vanilloid ligands anandamide and piperine, but not capsaicin, can reduce upper gastrointestinal motility. The effect of piperine involves capsaicin-sensitive neurons, but not vanilloid receptors, while the effect of anandamide involves **cannabinoid CB1**, but not vanilloid receptors.

IT **404-86-4**, Capsaicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(vanilloid receptor role in gastrointestinal transit control)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

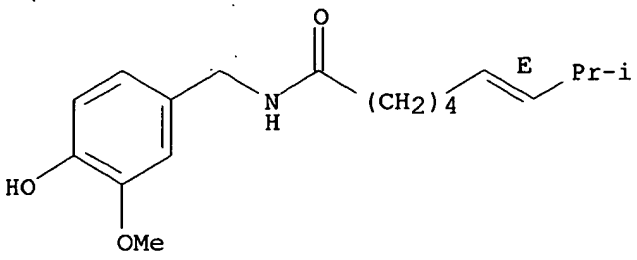
L11 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137736 HCAPLUS
DOCUMENT NUMBER: 134:335978
TITLE: Structure-activity relationship for the endogenous **cannabinoid**, anandamide, and certain of its analogues at vanilloid receptors in transfected cells and vas deferens
AUTHOR(S): Ross, Ruth A.; Gibson, T. Michael; Brockie, Heather C.; Leslie, Mark; Pashmi, Ghazaleh; Craib, Susan J.; Di Marzo, Vincenzo; Pertwee, Roger G.
CORPORATE SOURCE: Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, AB25 2ZD, UK
SOURCE: British Journal of Pharmacology (2001), 132(3), 631-640
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study was directed at exploring the structure-activity relation for anandamide and certain of its analogs at the rat VR1 receptor in transfected cells and at investigating the relative extent to which anandamide interacts with **CB1** and vanilloid receptors in the mouse vas deferens. PKi values for displacement of [3H]-resiniferatoxin from membranes of rVR1 transfected CHO cells were significantly less for anandamide (5.78) than for its structural analogs N-(4-hydroxyphenyl)-arachidonylamide (AM404; 6.18) and N-(3-methoxy-4-hydroxy)benzyl-arachidonylamide (arvanil; 6.77). PEC50 values for stimulating 45Ca2+ uptake into rVR1 transfected CHO cells were significantly less for anandamide (5.80) than for AM404 (6.32) or arvanil (9.29). Arvanil was also significantly more potent than capsaicin (pEC50 = 7.37), a compd. with the same substituted benzyl polar head group as arvanil. In the mouse vas deferens, resiniferatoxin was 218 times more potent than capsaicin as an inhibitor of elec.-evoked contractions. Both drugs were antagonized to a similar extent by capsazepine (pKB = 6.93 and 7.18 resp.) but were not antagonized by SR141716A (1 .mu.M). Anandamide was less susceptible than capsaicin to antagonism by capsazepine (pKB = 6.02) and less susceptible to antagonism by SR141716A (pKB = 8.66) than methanandamide (pKB = 9.56). WIN55212 was antagonized by SR141716A (pKB = 9.02) but not by capsazepine (10 .mu.M). In conclusion, anandamide and certain of its analogs have affinity and efficacy at the rat VR1 receptor. In the mouse vas deferens, which seems to express vanilloid and **CB1** receptors, both receptor types appear to contribute to anandamide-induced inhibition of evoked contractions.

IT **404-86-4**, Capsaicin **128007-31-8**, Arvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity relationship for anandamide and its analogs at vanilloid and **cannabinoid** receptors)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

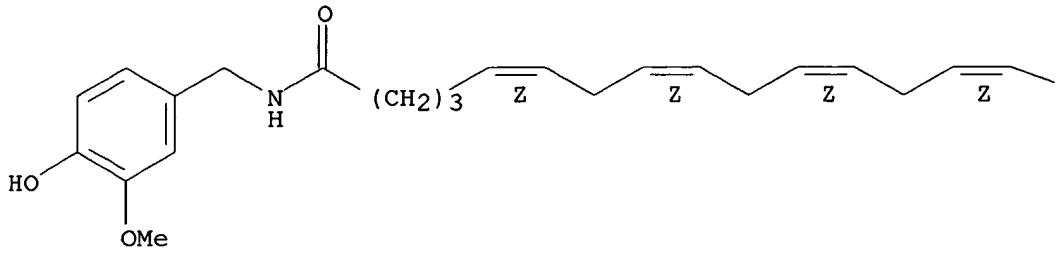
Double bond geometry as shown.



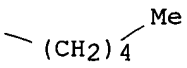
RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:122170 HCAPLUS
DOCUMENT NUMBER: 135:13846
TITLE: Highly Selective **CB1 Cannabinoid** Receptor Ligands and Novel **CB1**/VR1 Vanilloid Receptor "Hybrid" Ligands
AUTHOR(S): Di Marzo, V.; Bisogno, T.; De Petrocellis, L.; Brandi, I.; Jefferson, R. G.; Winckler, R. L.; Davis, J. B.; Dasse, O.; Mahadevan, A.; Razdan, R. K.; Martin, B. R.
CORPORATE SOURCE: Endocannabinoid Research Group, Istituto per la Chimica di Molecole di Interesse Biologico and Instituto di CiberneticaConsiglio Nazionale delle Ricerche, Arco Felice (NA), 80072, Italy
SOURCE: Biochemical and Biophysical Research Communications (2001), 281(2), 444-451

CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anandamide and the metabolically stabler analogs, (R)-1'-methyl-2'-hydroxy-ethyl-arachidonamide (Met-AEA) and N-(3-methoxy-4-hydroxy-benzyl)-arachidonamide (arvanil), are **CB1 cannabinoid** and VR1 vanilloid receptors agonists. We synthesized 1',1'-dimethylheptyl-arvanil (O-1839) and six other AEA analogs obtained by addn. of either a hydroxy, cyano, or bromo group on the C-20 atom of 1,1'-dimethylpentyl-Met-AEA (O-1811, O-1812 and O-1860, resp.) or 1,1'-dimethylpentyl-arvanil (O-1856, O-1895 and O-1861, resp.). The compds. were tested for their affinity for **CB1** and CB2 receptors, capability to activate VR1 receptors, inhibitory effect on the anandamide hydrolysis and on the anandamide membrane transporter, and cannabimimetic activity in the mouse 'tetrad' of in vivo assays. O-1812 is the first ligand ever proven to be highly (500- to 1000-fold) selective for **CB1** vs. both VR1 and CB2 receptors, while O-1861 is the first true "hybrid" agonist of **CB1**/VR1 receptors and a compd. with potential therapeutic importance. The activities of the seven compds. in vivo did not correlate with their activities at either **CB1** or VR1 receptors, thus suggesting the existence of other brain sites of action mediating some of their neurobehavioral actions in mice. (c) 2001 Academic Press.

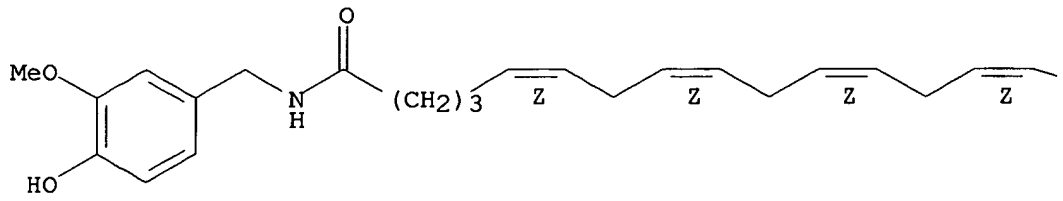
IT **322399-51-9**, O 1839 **322399-54-2**, O 1856
322399-59-7, O 1861 **322399-60-0**, O 1895
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(highly selective **CB1 cannabinoid** receptor ligands and novel **CB1**/VR1 vanilloid receptor Hybrid ligands)

RN 322399-51-9 HCAPLUS

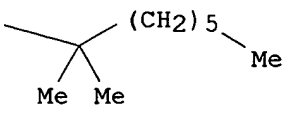
CN 5,8,11,14-Docosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

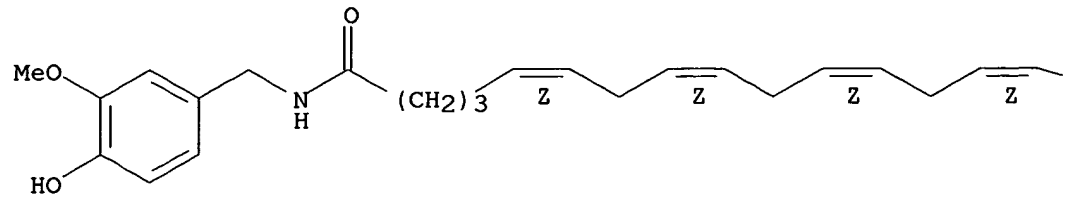


RN 322399-54-2 HCAPLUS

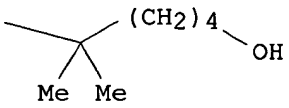
CN 5,8,11,14-Eicosatetraenamide, 20-hydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

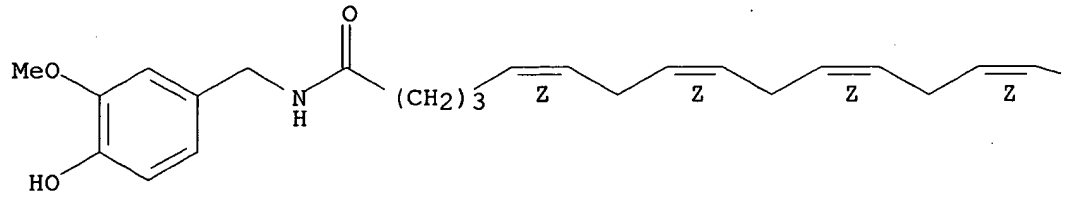


RN 322399-59-7 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, 20-bromo-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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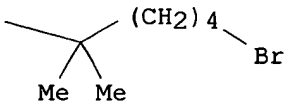
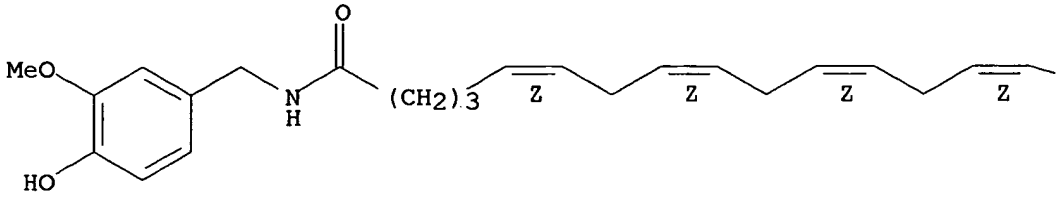


RN 322399-60-0 HCAPLUS

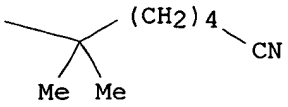
CN 5,8,11,14-Eicosatetraenamide, 20-cyano-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:736079 HCAPLUS
DOCUMENT NUMBER: 134:66067
TITLE: Neurobehavioral activity in mice of N-vanillyl-arachidonyl-amide
AUTHOR(S): Di Marzo, V.; Breivogel, C.; Bisogno, T.; Melck, D.; Patrick, G.; Tao, Q.; Szallasi, A.; Razdan, R. K.; Martin, B. R.
CORPORATE SOURCE: Consiglio Nazionale delle Ricerche, Istituto per la Chimica di Molecole di Interesse Biologico, Arco Felice, 80072, Italy
SOURCE: European Journal of Pharmacology (2000), 406(3), 363-374
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the cannabimimetic properties of N-vanillyl-arachidonoyl-amide (arvanil), a potential agonist of **cannabinoid CB1** and capsaicin VR1 receptors, and an inhibitor of the facilitated transport of the endocannabinoid anandamide. Arvanil and anandamide exhibited similar affinities for the **cannabinoid CB1** receptor, but arvanil was less efficacious in inducing **cannabinoid CB1** receptor-mediated GTP.gamma.S binding. The Ki of arvanil for the vanilloid VR1 receptor was 0.28 .mu.M. Administered i.v. to mice, arvanil was 100 times more potent than anandamide in producing hypothermia, analgesia, catalepsy and inhibiting spontaneous activity. These effects were not attenuated by the **cannabinoid CB1** receptor antagonist N-(piperidin-1-yl)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide.cntdot.HCl (SR141716A). Arvanil (i.t. administration) induced analgesia in the tail-flick test that was not

blocked by either SR141716A or the vanilloid VR1 antagonist capsazepine. Conversely, capsaicin was less potent as an analgesic (ED50 180 ng/mouse, i.t.) and its effects attenuated by capsazepine. The analgesic effect of anandamide (i.t.) was also unaffected by SR141716A but was 750-fold less potent (ED50 20.5 .mu.g/mouse) than capsaicin. These data indicate that the neurobehavioral effects exerted by arvanil are not due to activation of **cannabinoid CB1** or vanilloid VR1 receptors.

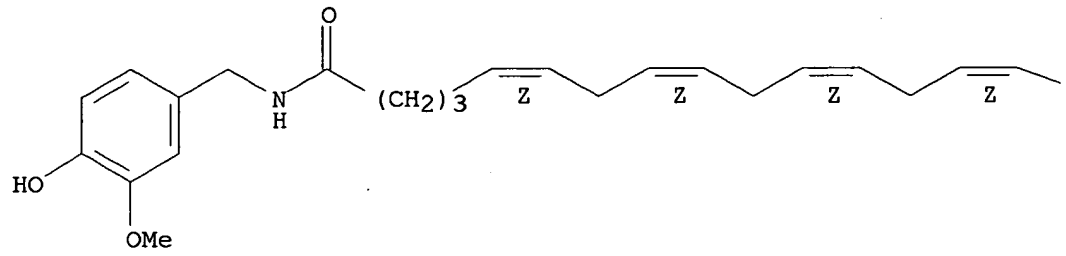
IT **128007-31-8**, Arvanil
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurobehavioral activity of N-vanillyl-arachidonyl-amide (arvanil) in mice)

RN 128007-31-8 HCAPLUS

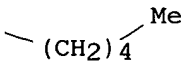
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:719974 HCAPLUS

DOCUMENT NUMBER: 134:50981

TITLE: Overlap between the ligand recognition properties of the anandamide transporter and the VR1 vanilloid receptor: inhibitors of anandamide uptake with negligible capsaicin-like activity

AUTHOR(S): De Petrocellis, L.; Bisogno, T.; Davis, J. B.; Pertwee, R. G.; Di Marzo, V.

CORPORATE SOURCE: Endocannabinoid Research Group, Istituto di Cibernetica, C.N.R., Arco Felice, Napoli, 80072, Italy

SOURCE: FEBS Letters (2000), 483(1), 52-56
CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier Science B.V.

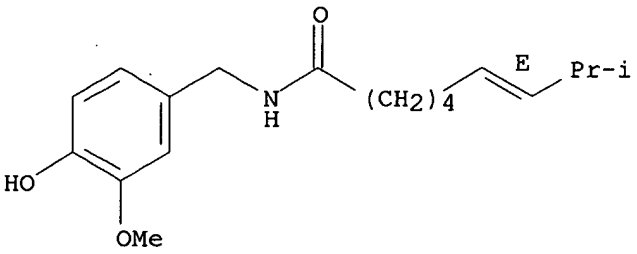
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Some synthetic agonists of the VR1 vanilloid (capsaicin) receptor also inhibit the facilitated transport into cells of the endogenous **cannabinoid** anandamide (arachidonoylethanolamide, AEA). Here we tested several AEA derivs. contg. various derivatized Ph groups or different alkyl chains as either inhibitors of the AEA membrane transporter (AMT) in intact cells or functional agonists of the VR1 vanilloid receptor in HEK cells transfected with the human VR1. We found that four known AMT inhibitors, AM404, arvanil, olvanil and linvanil, activate VR1 receptors at concns. 400-10000-fold lower than those necessary to inhibit the AMT. However, we also found three novel AEA derivs., named VDM11, VDM12 and VDM13, which inhibit the AMT as potently as AM404 but exhibit little or no agonist activity at hVR1. These compds. are weak inhibitors of AEA enzymic hydrolysis and poor **CB1**/CB2 receptor ligands. We show for the first time that, despite the overlap between the chem. moieties of AMT inhibitors and VR1 agonists, selective inhibitors of AEA uptake that do not activate VR1 (e.g. VDM11) can be developed.

IT **404-86-4**, Capsaicin **58493-49-5**, Olvanil
69693-13-6, Palvanil **104899-01-6**, Linvanil
104926-32-1 128007-31-8, Arvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(overlap between ligand recognition properties of anandamide transporter and VR1 vanilloid receptor)

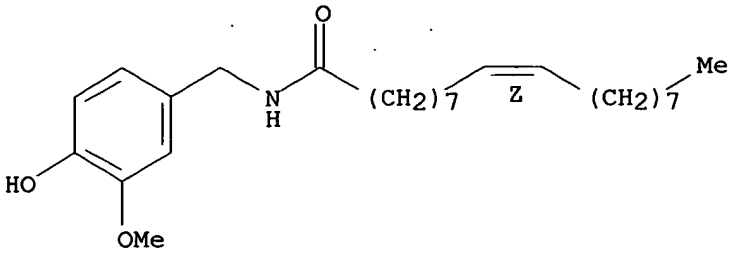
RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

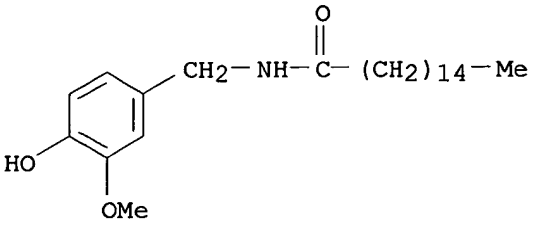


RN 58493-49-5 HCAPLUS
CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

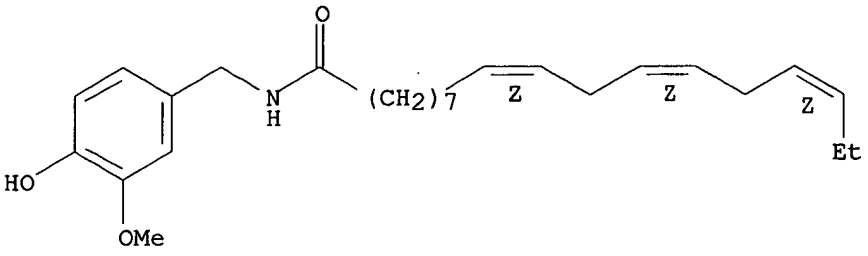


RN 69693-13-6 HCAPLUS
CN Hexadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



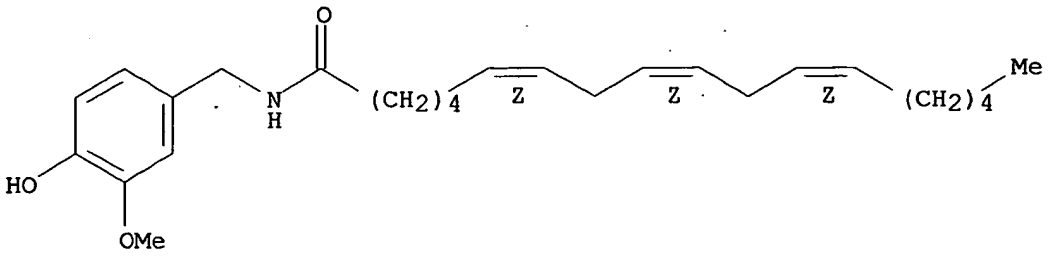
RN 104899-01-6 HCAPLUS
CN 9,12,15-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 104926-32-1 HCAPLUS
CN 6,9,12-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (6Z,9Z,12Z)- (9CI) (CA INDEX NAME)

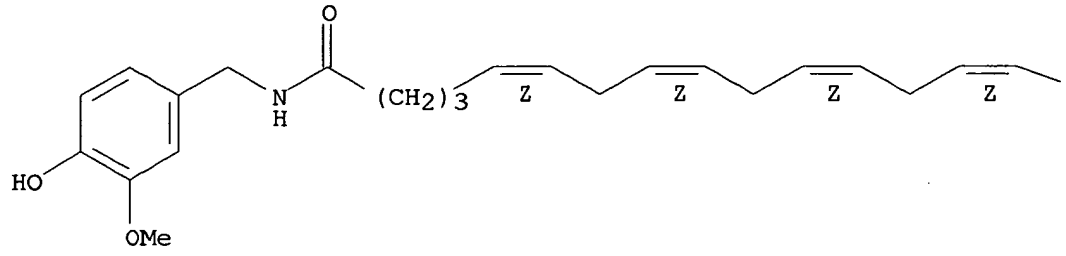
Double bond geometry as shown.



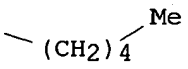
RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:209882 HCAPLUS
DOCUMENT NUMBER: 132:241970
TITLE: Pharmaceutical compositions containing N-acylvanillinamide derivatives capable of activating peripheral **cannabinoid** receptors
INVENTOR(S): Bisogno, Tiziana; Della Valle, Francesco; De Petrocellis, Luciano; Di Marzo, Vincenzo; Marcolongo, Gabriele; Melck, Dominique
PATENT ASSIGNEE(S): Innovet Italia S.r.l., Italy; Consiglio Nazionale Delle Ricerche
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000016756	A2	20000330	WO 1999-EP6980	19990921
WO 2000016756	A3	20000908		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 1302264	B1	20000905	IT 1998-MI2064	19980924
AU 9960860	A1	20000410	AU 1999-60860	19990921
EP 1115392	A2	20010718	EP 1999-947394	19990921
EP 1115392	B1	20021211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 229330	E	20021215	AT 1999-947394	19990921

PRIORITY APPLN. INFO.: IT 1998-MI2064 A 19980924
WO 1999-EP6980 W 19990921

OTHER SOURCE(S): MARPAT 132:241970

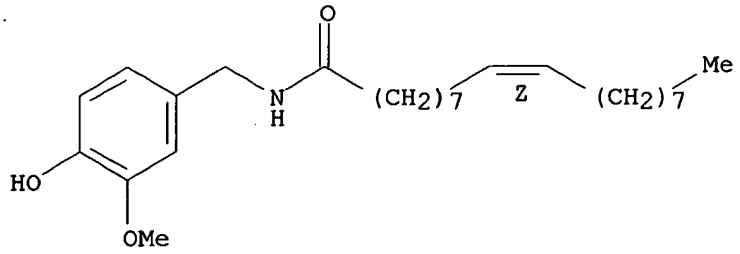
AB Pharmaceutical compns. contg. N-acylvanillinamide derivs. capable of activating the peripheral receptor **CB1** of **cannabinoids** (Markush structures) are disclosed. N-(4-hydroxy-3-methoxybenzyl)oleyalmide (I) was prepd. by the reaction of oleic acid, 4-methylmorpholine, and 4-hydroxy-3-methoxybenzylmine hydrochloride. The specific binding of I to mouse neuroblastoma cells and rat leukemia basophil cell was 1.64 .mu.M and >15 .mu.M, resp. A tablet contained 30, lactose 85, corn starch 75, talc 6, magnesium stearate 2, and CM-cellulose 2 mg.

IT **58493-49-5P 69693-13-6P 128007-31-8P 261946-50-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. contg. N-acylvanillinamide derivs. capable of activating peripheral **cannabinoid** receptors)

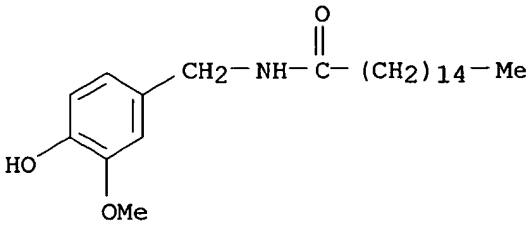
RN 58493-49-5 HCAPLUS

CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



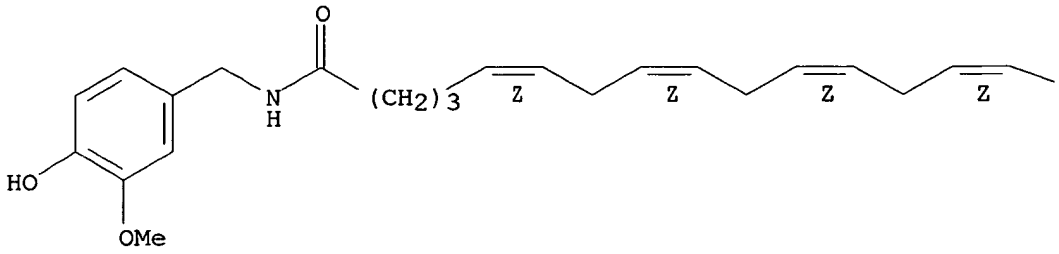
RN 69693-13-6 HCAPLUS
CN Hexadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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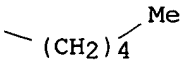
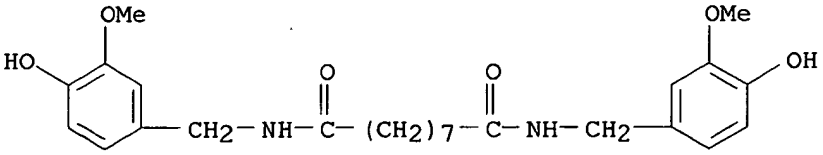


RN 261946-50-3 HCAPLUS
CN Nonanediamide, N,N'-bis[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



L11 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:4740 HCAPLUS

DOCUMENT NUMBER: 132:132746
TITLE: Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation
AUTHOR(S): Melck, Dominique; De Petrocellis, Luciano; Orlando, Pierangelo; Bisogno, Tiziana; Laezza, Chiara; Bifulco, Maurizio; Di Marzo, Vincenzo
CORPORATE SOURCE: Istituto per la Chimica di Molecole di Interesse Biologico, Consiglio Nazionale delle Ricerche, Arco Felice, 80072, Italy
SOURCE: Endocrinology (2000), 141(1), 118-126
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

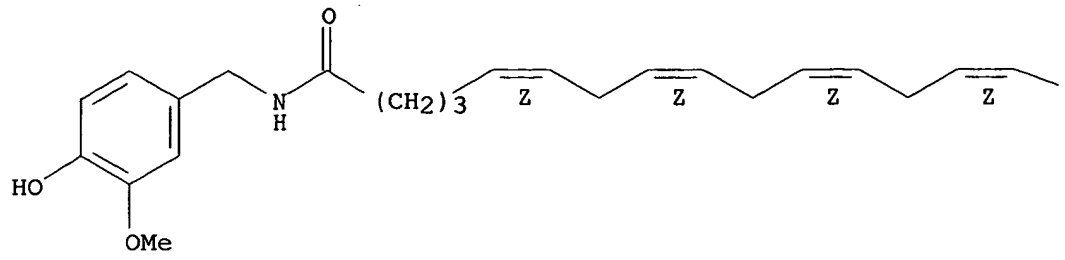
AB Anandamide and 2-arachidonoylglycerol (2-AG), two endogenous ligands of the **CB1** and CB2 **cannabinoid** receptor subtypes, inhibit the proliferation of PRL-responsive human breast cancer cells (HBCCs) through down-regulation of the long form of the PRL receptor (PRLr). Here the authors report that (1) anandamide and 2-AG inhibit the nerve growth factor (NGF)-induced proliferation of HBCCs through suppression of the levels of NGF Trk receptors; (2) inhibition of PRLr levels results in inhibition of the proliferation of other PRL-responsive cells, the prostate cancer DU-145 cell line; and (3) **CB1**-like **cannabinoid** receptors are expressed in HBCCs and DU-145 cells and mediate the inhibition of cell proliferation and Trk/PRLr expression. .beta.-NGF-induced HBCC proliferation was potently inhibited (IC50 = 50-600 nM) by the synthetic **cannabinoid** HU-210, 2-AG, anandamide, and its metabolically stable analogs, but not by the anandamide congener, palmitoylethanolamide, or the selective agonist of CB2 **cannabinoid** receptors, BML-190. The effect of anandamide was blocked by the **CB1** receptor antagonist, SR141716A, but not by the CB2 receptor antagonist, SR144528. Anandamide and HU-210 exerted a strong inhibition of the levels of NGF Trk receptors as detected by Western immunoblotting; this effect was reversed by SR141716A. When induced by exogenous PRL, the proliferation of prostate DU-145 cells was potently inhibited (IC50 = 100-300 nM) by anandamide, 2-AG, and HU-210. Anandamide also down-regulated the levels of PRLr in DU-145 cells. SR141716A attenuated these two effects of anandamide. HBCCs and DU-145 cells were shown to contain (1) transcripts for **CB1** and, to a lesser extent, CB2 **cannabinoid** receptors, (2) specific binding sites for [3H]SR141716A that could be displaced by anandamide, and (3) a **CB1** receptor-immunoreactive protein. These findings suggest that endogenous **cannabinoids** and **CB1** receptor agonists are potential neg. effectors of PRL- and NGF-induced biol. responses, at least in some cancer cells.

IT **128007-31-8**, Arvanil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate cancer cell proliferation)

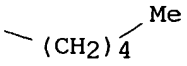
RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:547817 HCAPLUS
DOCUMENT NUMBER: 131:295454
TITLE: Local administration of .DELTA.9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys: a peripheral **cannabinoid** action
AUTHOR(S): Ko, Mei-Chuan; Woods, James H.
CORPORATE SOURCE: Department of Pharmacology, Medical School, University of Michigan, Ann Arbor, MI, 48109-0632, USA
SOURCE: Psychopharmacology (Berlin) (1999), 143(3), 322-326
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rationale: **Cannabinoids** can reduce nociceptive responses by acting on peripheral **cannabinoid** receptors in rodents. Objectives: The study was conducted to evaluate the hypothesis that local administration of .DELTA.9-tetrahydrocannabinol (.DELTA.9-THC) can attenuate capsaicin-induced nociception in rhesus monkeys. Methods: Capsaicin (100 .mu.g) was applied locally in the tail of rhesus monkeys to evoke a nociceptive response, thermal allodynia, in normally innocuous 46 water. .DELTA.9-THC (10-320 .mu.g) was coadministered with capsaicin in the tail to assess local antinociceptive effects. In addn., a local antagonism study was performed to confirm the selectivity of .DELTA.9-THC action. Results: .DELTA.9-THC dose-dependently inhibited capsaicin-induced allodynia. This local antinociception was antagonized by small doses (10-100 .mu.g) of the **cannabinoid CB1** antagonist, SR141716A, applied in the tail. However, 100 .mu.g SR141716A injected s.c. in the back did not antagonize local .DELTA.9-THC. Conclusions: These results indicate that the site of action of locally

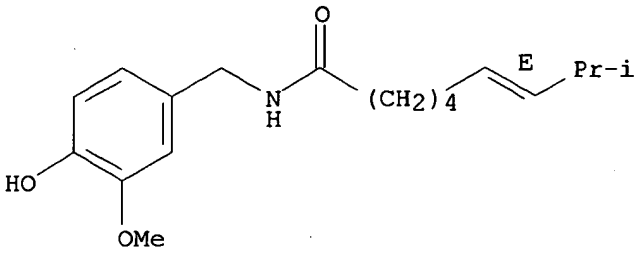
applied .DELTA.9-THC is in the tail. It provides functional evidence that activation of peripheral **cannabinoid CB1** receptors can attenuate capsaicin-induced thermal nociception in non-human primates and suggests a new approach for **cannabinoids** in pain management.

IT **404-86-4**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(local administration of .DELTA.9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys)

RN 404-86-4 HCAPLUS

CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:510255 HCAPLUS

DOCUMENT NUMBER: 131:295096

TITLE: Unsaturated Long-Chain N-Acyl-vanillyl-amides (N-AVAMs): Vanilloid Receptor Ligands That Inhibit Anandamide-Facilitated Transport and Bind to **CB1 Cannabinoid** Receptors

AUTHOR(S): Melck, Dominique; Bisogno, Tiziana; De Petrocellis, Luciano; Chuang, Huai-hu; Julius, David; Bifulco, Maurizio; Di Marzo, Vincenzo

CORPORATE SOURCE: Istituto per la Chimica di Molecole di Interesse Biologico, Consiglio Naz. Ric., Arco Felice, Napoli, 80072, Italy

SOURCE: Biochemical and Biophysical Research Communications (1999), 262(1), 275-284
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

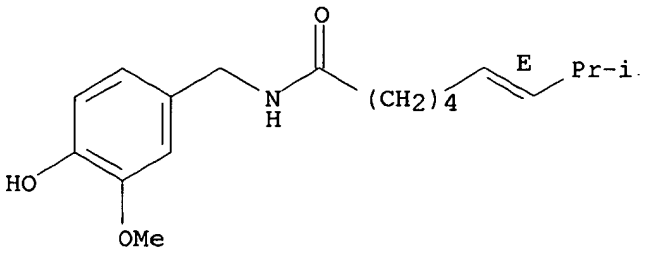
AB We investigated the effect of changing the length and degree of unsatn. of the fatty acyl chain of N-(3-methoxy-4-hydroxy)-benzyl-cis-9-octadecenoamide (olvanil), a ligand of vanilloid receptors, on its capability to: (i) inhibit anandamide-facilitated transport into cells and enzymic hydrolysis, (ii) bind to **CB1** and CB2 **cannabinoid** receptors, and (iii) activate the VR1 vanilloid receptor. Potent inhibition of [14C]anandamide accumulation into cells was achieved with C20:4 n-6, C18:3 n-6 and n-3, and C18:2 n-6 N-acyl-vanillyl-amides (N-AVAMs). The satd. analogs and .DELTA.9-trans-olvanil were inactive. Activity in **CB1** binding assays increased when increasing the no.

of cis-double bonds in a n-6 fatty acyl chain and, in satd. N-AVAMs, was not greatly sensitive to decreasing the chain length. The C20:4 n-6 analog (arvanil) was a potent inhibitor of anandamide accumulation (IC50 = 3.6 .mu.M) and was 4-fold more potent than anandamide on **CB1** receptors (Ki = 0.25-0.52 .mu.M), whereas the C18:3 n-3 N-AVAM was more selective than arvanil for the uptake (IC50 = 8.0 .mu.M) vs. **CB1** receptors (Ki = 3.4 .mu.M). None of the compds. efficiently inhibited [14C]anandamide hydrolysis or bound to CB2 receptors. All N-AVAMs activated the cation currents coupled to VR1 receptors overexpressed in Xenopus oocytes. In a simple, intact cell model of both vanilloid- and anandamide-like activity, i.e., the inhibition of human breast cancer cell (HBCC) proliferation, arvanil was shown to behave as a "hybrid" activator of **cannabinoid** and vanilloid receptors. (c) 1999 Academic Press.

IT **404-86-4**, Capsaicin **2444-46-4**, Pseudocapsaicin
16729-47-8 58493-49-5, Olvanil **58493-50-8**
69693-13-6 95548-23-5 104899-01-6
104926-32-1 128007-31-8 152919-36-3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(unsatd. long-chain N-acyl-vanillyl-amides as vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to **CB1 cannabinoid** receptors)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 2444-46-4 HCAPLUS
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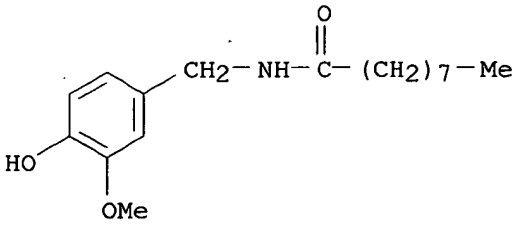

RN 16729-47-8 HCAPLUS
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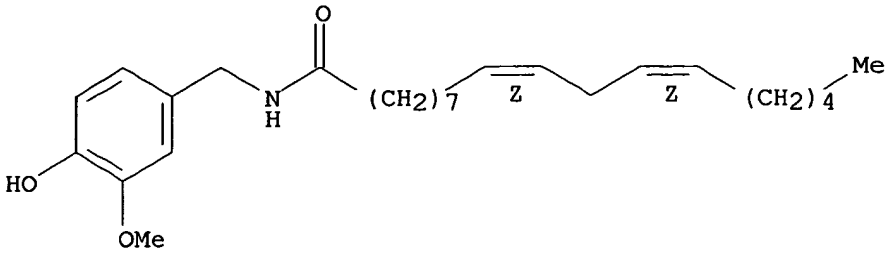
(9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 58493-49-5 HCAPLUS
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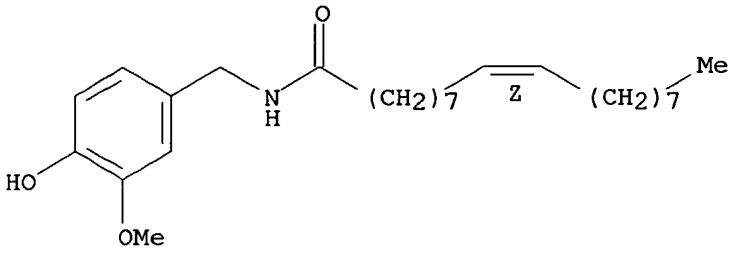
Double bond geometry as shown.



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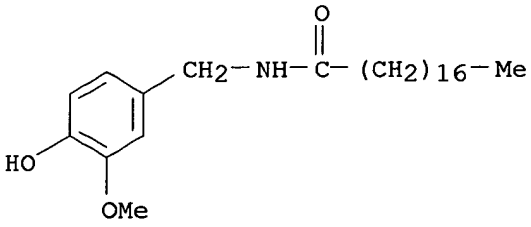

RN 69693-13-6 HCAPLUS
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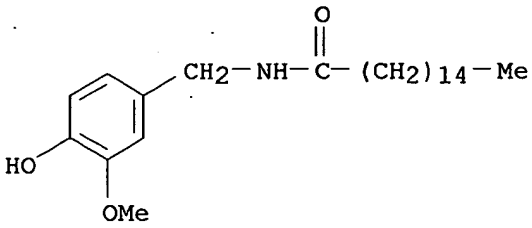

RN 95548-23-5 HCAPLUS
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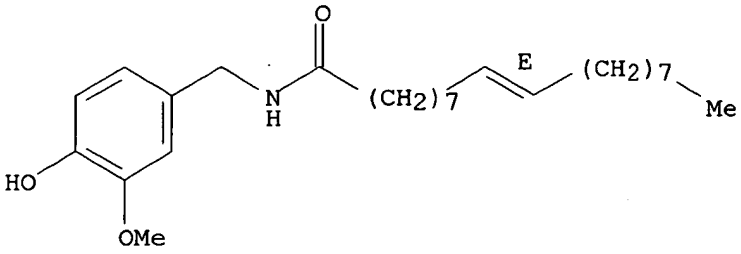
Double bond geometry as shown.



RN 104899-01-6 HCAPLUS
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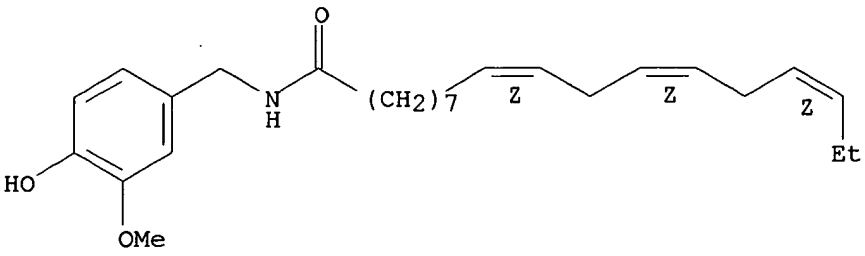

RN 104926-32-1 HCAPLUS
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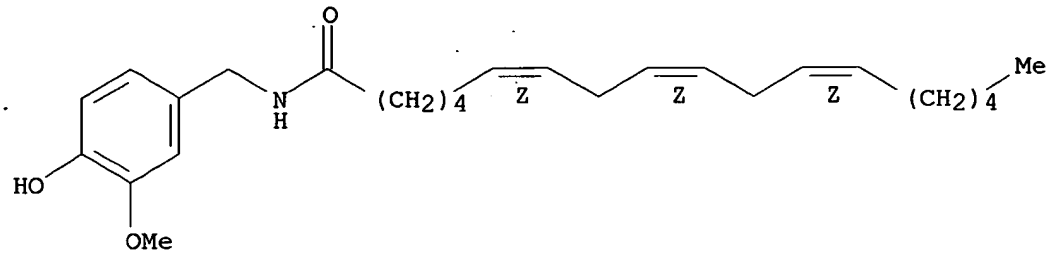
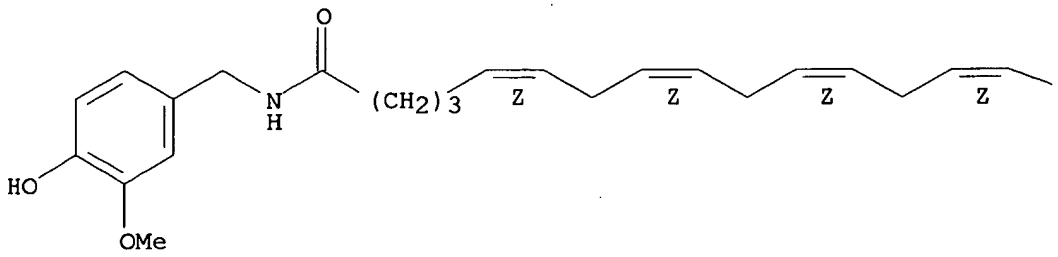
Double bond geometry as shown.



RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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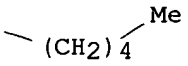

RN 152919-36-3 HCAPLUS
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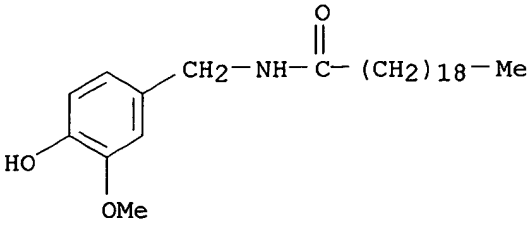

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:505507 HCAPLUS
DOCUMENT NUMBER: 131:266901
TITLE: Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide
AUTHOR(S): Zygmunt, Peter M.; Petersson, Jesper; Andersson, David A.; Chuang, Huai-Hu; Sorgard, Morten; Di Marzo, Vincenzo; Julius, David; Hogestatt, Edward D.
CORPORATE SOURCE: Department of Clinical Pharmacology, Institute of Laboratory Medicine, University of Lund, Lund, S-221 85, Swed.
SOURCE: Nature (London) (1999), 400(6743), 452-457
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endogenous **cannabinoid** receptor agonist anandamide is a powerful vasodilator of isolated vascular prepns., but its mechanism of action is unclear. Here we show that the vasodilator response to anandamide in isolated arteries is capsaicin-sensitive and accompanied by release of calcitonin-gene-related peptide (CGRP). The selective CGRP-receptor antagonist 8-37 CGRP, but not the **cannabinoid** **CB1** receptor blocker SR141716A, inhibited the vasodilator effect of anandamide. Other endogenous (2-arachidonylglycerol, palmitylethanolamide) and synthetic (HU 210, WIN 55,212-2, CP 55,940) **CB1** and CB2 receptor agonists could not mimic the action of anandamide. The selective vanilloid receptor antagonist capsazepine inhibited anandamide-induced vasodilation and release of CGRP. In patch-clamp expts. on cells expressing the cloned vanilloid receptor (VR1), anandamide induced a capsazepine-sensitive current in whole cells and isolated membrane patches. Our results indicate that anandamide induces vasodilation by activating vanilloid receptors on perivascular sensory nerves and causing release of CGRP. The vanilloid receptor may thus be another mol. target for endogenous anandamide, besides **cannabinoid** receptors, in the nervous and cardiovascular systems.

IT **404-86-4**, Capsaicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(mechanism of anandamide vasodilation through activation of vanilloid receptors on perivascular sensory nerves and CGRP release)

RN 404-86-4 HCAPLUS
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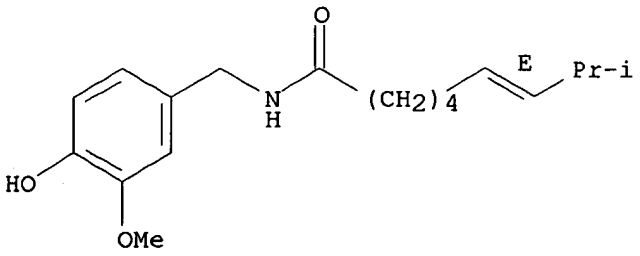
Double bond geometry as shown.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

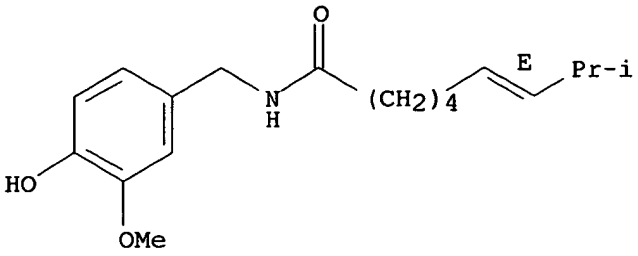
L11 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:698015 HCAPLUS
DOCUMENT NUMBER: 130:76092
TITLE: Interactions between synthetic vanilloids and the endogenous **cannabinoid** system
AUTHOR(S): Di Marzo, Vincenzo; Bisogno, Tiziana; Melck, Dominique; Ross, Ruth; Brockie, Heather; Stevenson, Lesley; Pertwee, Roger; De Petrocellis, Luciano
CORPORATE SOURCE: Istituto per la Chimica di Molecole di Interesse Biologico, CNR, Arco Felice, 80072, Italy
SOURCE: FEBS Letters (1998), 436(3), 449-454
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chem. similarity between some synthetic agonists of vanilloid receptors, such as olvanil (N-vanillyl-cis-9-octadecenoamide), and the 'endocannabinoid' anandamide (arachidonoyl-ethanolamide, AEA), suggests possible interactions between the **cannabinoid** and vanilloid signalling systems. Here the authors report that olvanil is a stable and potent inhibitor of AEA facilitated transport into rat basophilic leukemia (RBL-2H3) cells. Olvanil blocked both the uptake and the hydrolysis of [14C]AEA by intact RBL-2H3 cells (IC50 = 9 .mu.M), while capsaicin and pseudocapsaicin (N-vanillyl-nonanamide) were much less active. Olvanil was more potent than previously reported inhibitors of AEA facilitated transport, i.e. phloretin (IC50 = 80 .mu.M), AM404 (12.9%, inhibition at 10 .mu.M) or oleoylethanolamide (27.5% inhibition at 10 .mu.M). Olvanil was a poor inhibitor of [14C]AEA hydrolysis by RBL-2H3 and N18TG2 cell membranes, suggesting that the inhibitory effect on [14C]AEA breakdown obsd. in intact cells was due to inhibition of [14C]AEA uptake. Olvanil was stable to enzymic hydrolysis, and (i) displaced the binding of high affinity **cannabinoid** receptor ligands to membrane prepns. from N18TG2 cells and guinea pig forebrain (Ki = 1.64-7.08 .mu.M), but not from cells expressing the CB2 **cannabinoid** receptor subtype; (ii) inhibited forskolin-induced cAMP formation in intact N18TG2 cells (IC50 = 1.60 .mu.M), this effect being reversed by the selective **CB1** antagonist SR141716A. Pseudocapsaicin, but not capsaicin, also selectively bound to **CB1** receptor-contg. membranes. These data suggest that some of the analgesic actions of olvanil may be due to its interactions with the endogenous **cannabinoid** system, and may lead to the design of a novel class of cannabimimetics with potential therapeutic applications as analgesics.

IT **404-86-4**, Capsaicin **2444-46-4**, Pseudocapsaicin
58493-49-5, Olvanil
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interactions between synthetic vanilloids and the endogenous **cannabinoid** system)

RN 404-86-4 HCAPLUS
CN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (6E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 2444-46-4 HCAPLUS
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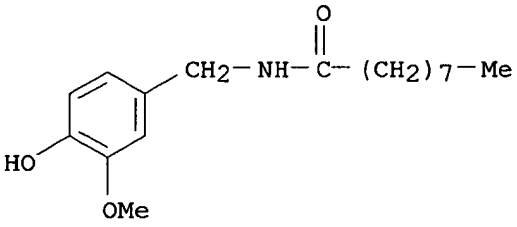

RN 58493-49-5 HCAPLUS
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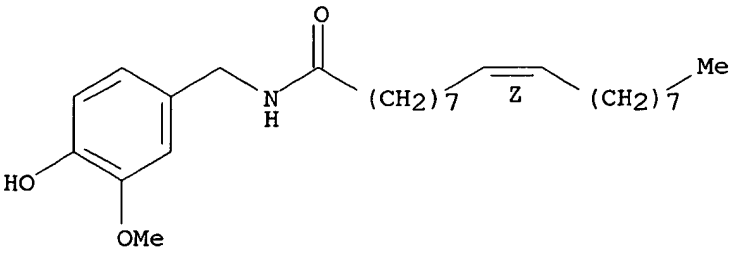
Double bond geometry as shown.



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 NEWS  3  Jun 03   New e-mail delivery for search results now available
 NEWS  4  Aug 08   PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS  5  Aug 19   Aquatic Toxicity Information Retrieval (AQUIRE)
                   now available on STN
 NEWS  6  Aug 26   Sequence searching in REGISTRY enhanced
 NEWS  7  Sep 03   JAPIO has been reloaded and enhanced
 NEWS  8  Sep 16   Experimental properties added to the REGISTRY file
 NEWS  9  Sep 16   CA Section Thesaurus available in CAPLUS and CA
 NEWS 10  Oct 01   CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 11  Oct 24   BEILSTEIN adds new search fields
 NEWS 12  Oct 24   Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 13  Nov 18   DKILIT has been renamed APOLLIT
 NEWS 14  Nov 25   More calculated properties added to REGISTRY
 NEWS 15  Dec 04   CSA files on STN
 NEWS 16  Dec 17   PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 17  Dec 17   TOXCENTER enhanced with additional content
 NEWS 18  Dec 17   Adis Clinical Trials Insight now available on STN
 NEWS 19  Jan 29   Simultaneous left and right truncation added to COMPENDEX,
                   ENERGY, INSPEC
 NEWS 20  Feb 13   CANCERLIT is no longer being updated
 NEWS 21  Feb 24   METADEX enhancements
 NEWS 22  Feb 24   PCTGEN now available on STN
 NEWS 23  Feb 24   TEMA now available on STN
 NEWS 24  Feb 26   NTIS now allows simultaneous left and right truncation
 NEWS 25  Feb 26   PCTFULL now contains images
 NEWS 26  Mar 04   SDI PACKAGE for monthly delivery of multifile SDI results
 NEWS 27  Mar 19   APOLLIT offering free connect time in April 2003
 NEWS 28  Mar 20   EVENTLINE will be removed from STN
 NEWS 29  Mar 24   PATDPAFULL now available on STN
 NEWS 30  Mar 24   Additional information for trade-named substances without
                   structures available in REGISTRY
 NEWS 31  Apr 11   Display formats in DGENE enhanced
 NEWS 32  Apr 14   MEDLINE Reload
 NEWS 33  Apr 17   Polymer searching in REGISTRY enhanced
 NEWS 34  Apr 21   Indexing from 1947 to 1956 being added to records in CA/CAPLUS
 NEWS 35  Apr 21   New current-awareness alert (SDI) frequency in
                   WPIDS/WPINDEX/WPIX
 NEWS 36  Apr 28   RDISCLOSURE now available on STN
 NEWS 37  May 05   Pharmacokinetic information and systematic chemical names
                   added to PHAR

 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
```

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 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *


FILE 'HOME' ENTERED AT 13:43:09 ON 08 MAY 2003

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 13:43:22 ON 08 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     6 MAY 2003  HIGHEST RN 511508-58-0
DICTIONARY FILE UPDATES:    6 MAY 2003  HIGHEST RN 511508-58-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09787764-2.str

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
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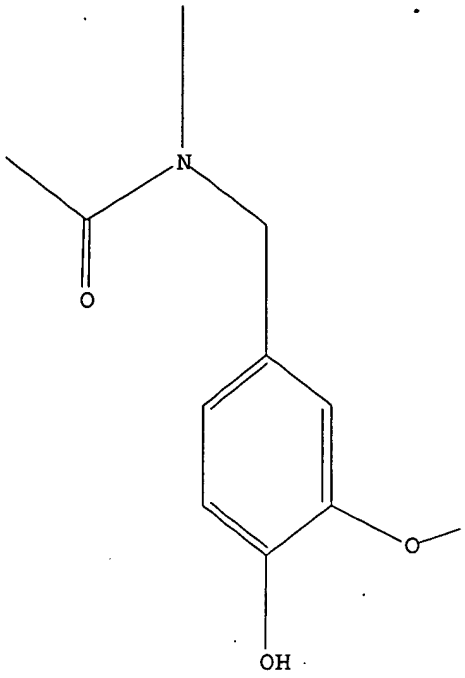

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 sss sam
SAMPLE SEARCH INITIATED 13:43:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    312 TO ITERATE

100.0% PROCESSED     312 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         5181 TO     7299
PROJECTED ANSWERS:               1 TO       80

L2            1 SEA SSS SAM L1

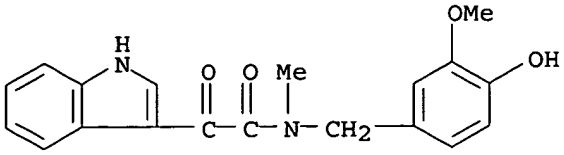
=> s l1 sss full
FULL SEARCH INITIATED 13:44:09 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   6405 TO ITERATE

100.0% PROCESSED    6405 ITERATIONS                               11 ANSWERS
SEARCH TIME: 00.00.01

L3           11 SEA SSS FUL L1

=> d scan

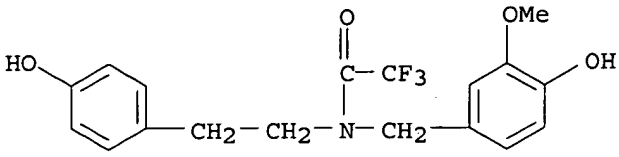
L3   11 ANSWERS   REGISTRY  COPYRIGHT 2003 ACS
IN   1H-Indole-3-acetamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl-
     .alpha.-oxo- (9CI)
MF   C19 H18 N2 O4
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

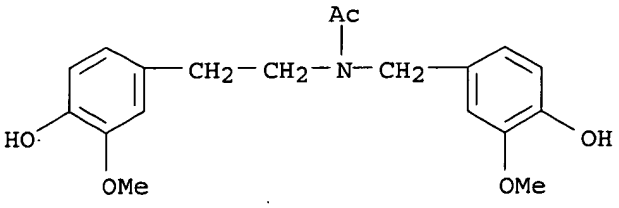
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Acetamide, 2,2,2-trifluoro-N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-[2-(4-hydroxyphenyl)ethyl]- (9CI)
MF C18 H18 F3 N O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

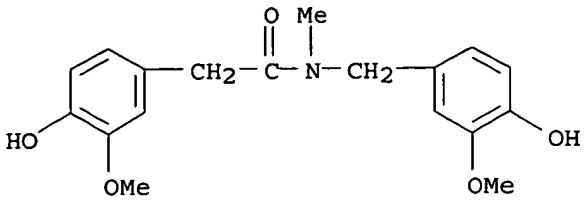
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Acetamide, N-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI)
MF C19 H23 N O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

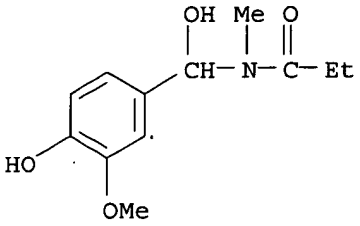
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzeneacetamide, 4-hydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl]-3-methoxy-N-methyl- (9CI)
MF C18 H21 N O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

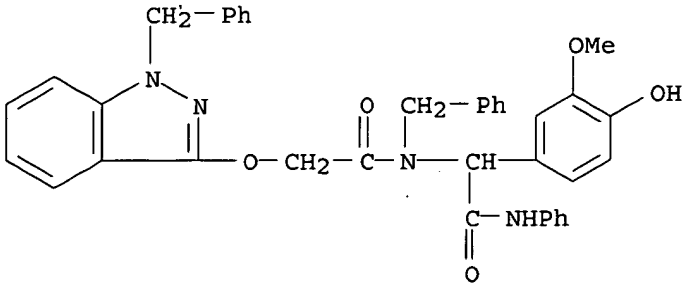
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Propanamide, N-[hydroxy(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl- (9CI)
MF C12 H17 N O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzeneacetamide, 4-hydroxy-3-methoxy-N-phenyl-.alpha.-[(phenylmethyl)[[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]acetyl]amino]- (9CI)
MF C38 H34 N4 O5



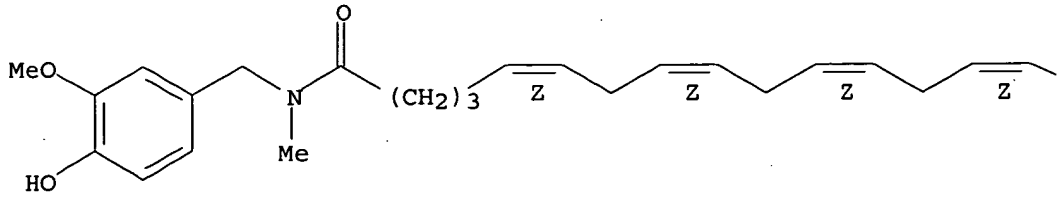
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

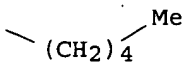
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl-, (5Z,8Z,11Z,14Z)- (9CI)
MF C29 H43 N O3

Double bond geometry as shown.

PAGE 1-A



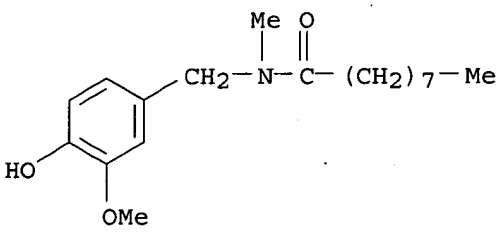
PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

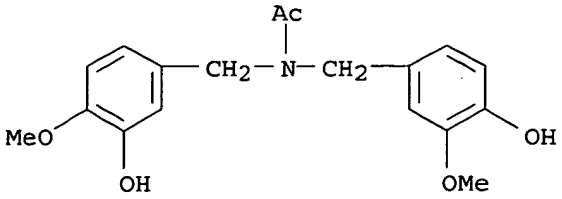
L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Nonanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl- (9CI)
MF C18 H29 N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Acetamide, N-[(3-hydroxy-4-methoxyphenyl)methyl]-N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI)
MF C18 H21 N O5

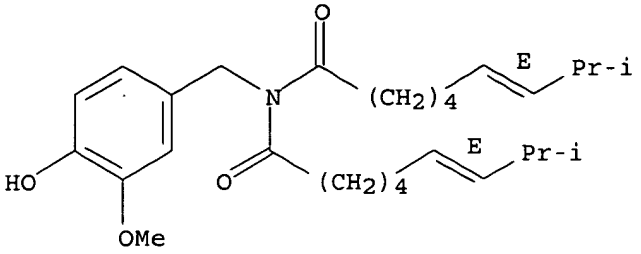


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 6-Nonenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-N-(8-methyl-1-oxo-6-nonenyl)-, (E,E)- (9CI)
MF C28 H43 N O4

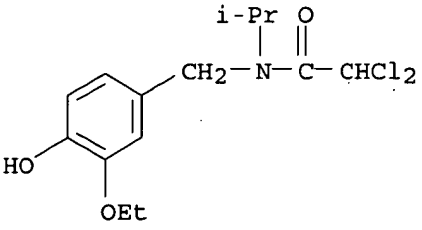
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 11 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Acetamide, 2,2-dichloro-N-[(3-ethoxy-4-hydroxyphenyl)methyl]-N-(1-methylethyl)- (9CI)
MF C14 H19 Cl2 N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> 1
1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

FULL ESTIMATED COST 148.95 149.16

FILE 'CAPLUS' ENTERED AT 13:45:01 ON 08 MAY 2003
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 8 May 2003 VOL 138 ISS 19
FILE LAST UPDATED: 7 May 2003 (20030507/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l3
L4          10 L3

=> s l4 and (receptor or CB1 or cannabinoid)
        510540 RECEPTOR
        466647 RECEPTORS
        608028 RECEPTOR
                  (RECEPTOR OR RECEPTORS)
          1547 CB1
          4164 CANNABINOID
          3479 CANNABINOIDS
          4912 CANNABINOID
                  (CANNABINOID OR CANNABINOIDS)
L5           3 L4 AND (RECEPTOR OR CB1 OR CANNABINOID)

=> s l5 and treat?
       2880786 TREAT?
L6           0 L5 AND TREAT?

=> dis l5 1-3 bib abs hitstr

L5   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:203609  CAPLUS
DN   137:56979
TI   A structure/activity relationship study on arvanil, an endocannabinoid and
     vanilloid hybrid
AU   Di Marzo, Vincenzo; Griffin, Graeme; De Petrocellis, Luciano; Brandi,
     Ines; Bisogno, Tiziana; Williams, William; Grier, Mark C.; Kulasegram,
     Sanjitha; Mahadevan, Anu; Razdan, Raj K.; Martin, Billy R.
CS   Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Naples,
     Italy
SO   Journal of Pharmacology and Experimental Therapeutics (2002), 300(3),
     984-991
     CODEN: JPETAB; ISSN: 0022-3565
PB   American Society for Pharmacology and Experimental Therapeutics
DT   Journal
LA   English
OS   CASREACT 137:56979
AB   Arvanil, a structural "hybrid" between the endogenous cannabinoid
     CB1 receptor ligand anandamide and capsaicin, is a
```

potent agonist for the capsaicin **receptor** VR1 (vanilloid **receptor** type 1), inhibits the anandamide membrane transporter (AMT), and induces cannabimimetic responses in mice. Novel arvanil derivs. prepd. by N-methylation, replacement of the amide with urea and thiourea moieties, and manipulation of the vanillyl group were evaluated for their ability to bind/activate **CB1 receptors**, activate VR1 **receptors**, inhibit the AMT and fatty acid amide hydrolase (FAAH), and produce cannabimimetic effects in mice. The compds. did not stimulate the **CB1 receptor**. Methylation of the amide group decreased the activity at VR1, AMT, and FAAH. On the arom. ring, the substitution of the 3-methoxy group with a chlorine atom or the lack of the 4-hydroxy group decreased the activity on VR1 and AMT, but not the affinity for **CB1 receptors**, and increased the capability to inhibit FAAH. The urea or thiourea analogs retained activity at VR1 and AMT but exhibited little affinity for **CB1 receptors**. The urea analog was a potent FAAH inhibitor (IC50 = 2.0 .mu.M). A water-sol. analog of arvanil, O-2142, was as active on VR1, much less active on AMT and **CB1**, and more potent on FAAH. All compds. induced a response in the mouse "tetrad", particularly those with EC50 <10 nM on VR1. However, the most potent compd., N-N'-di-(3-chloro-4-hydroxy)benzyl-arachidonamide (O-2093, ED50 .apprx.0.04 mg/kg), did not activate VR1 or **CB1 receptors**. Our findings suggest that VR1 and/or as yet uncharacterized **receptors** produce cannabimimetic responses in mice in vivo.

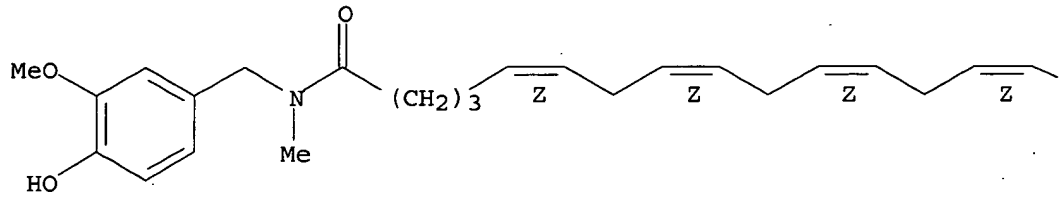
IT **439079-98-8P**, O 1988
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure/activity relationship study on arvanil)

RN 439079-98-8 CAPLUS

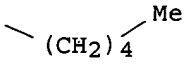
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 1995:715708 CAPLUS

DN 123:160081

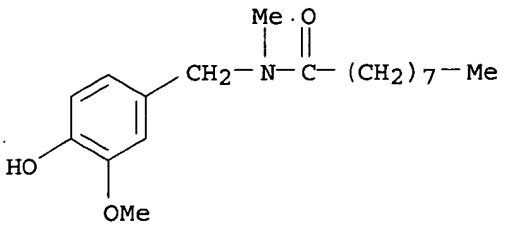
TI Quantitative structure-agonist activity relationship of capsaicin analogs

AU Klopman, Gilles; Li, Ju-Yun

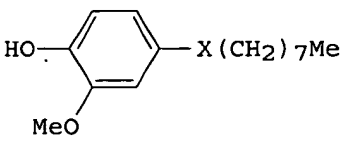
CS Department Chemistry, Case Western Reserve University, Cleveland, OH, 44106-7078, USA

SO Journal of Computer-Aided Molecular Design (1995), 9(3), 283-94

CODEN: JCADEQ; ISSN: 0920-654X
PB ESCOM
DT Journal
LA English
AB The MULTIple Computer Automated Structure Evaluation (MULTICASE) methodol. has been used to study the quant. structure-agonist activity relation of a series of capsaicin agonists. A no. of substructures and physicochem. properties of capsaicin analogs were identified as being responsible for high agonist potency. The optimal log P value for the agonist potency as estd. from QSAR anal. is 5.12. It was also found that a cluster of inactive mols. in the database have lipophilicity values below 2.94. Mol. modeling was employed to elucidate the detailed structural features of the pharmacophore of capsaicin analogs. Systematic conformational anal. has shown that the activity of capsaicin analogs strongly depends upon their ability to reach the required conformational profile. Based upon these observations, a three-dimensional pharmacophore model for the capsaicin-**receptor** interactions is proposed.
IT **150058-94-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(quant. structure-agonist activity relationship of capsaicin analogs)
RN 150058-94-9 CAPLUS
CN Nonanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl- (9CI) (CA INDEX NAME)



L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 1993:560600 CAPLUS
DN 119:160600
TI Analogs of capsaicin with agonist activity as novel analgesic agents; structure-activity studies. 2. The amide bond "B-region"
AU Walpole, Christopher S. J.; Wrigglesworth, Roger; Bevan, Stuart; Campbell, Elizabeth A.; Dray, Andy; James, Iain F.; Masdin, Kay J.; Perkins, Martin N.; Winter, Janet
CS Sandoz Inst. Med. Res., London, WC1E 6BN, UK
SO Journal of Medicinal Chemistry (1993), 36(16), 2373-80
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI



I

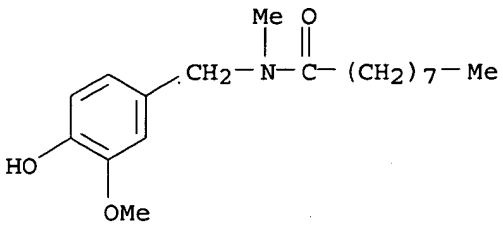
AB A series of compds. incorporating replacements for the amide bond "B-region" moiety of capsaicin were synthesized, including vanillylamides

and esters, homovanillic acid amides and esters, ureas, and thioureas, e.g. I (X = CONH, CH2NHCSNH, CH2CH2CO, CH:CHCO). These have been tested in an in vitro assay for agonism (45Ca2+ influx into dorsal root ganglia neurons), which is predictive of analgesic activity, to investigate the requirements in this region of capsaicin for activity. N-(4-Hydroxy-3-methoxybenzyl)-N'-octylthiourea emerged as the most potent analog (EC50 = 0.06 .mu.M). An operational model based on multiple hydrogen-bonding interactions is proposed to explain the structure-activity profile obsd. In combination with studies on the other regions of the capsaicin mol. these results describe a picture of the mol. interactions of capsaicin with its putative **receptor**.

IT **150058-94-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of, with nonanoyl chloride)

RN 150058-94-9 CAPLUS

CN Nonanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl- (9CI) (CA INDEX NAME)




```
=> dis hist

     (FILE 'HOME' ENTERED AT 13:43:09 ON 08 MAY 2003)

     FILE 'REGISTRY' ENTERED AT 13:43:22 ON 08 MAY 2003
L1               STRUCTURE UPLOADED
L2             1 S L1 SSS SAM
L3            11 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:45:01 ON 08 MAY 2003
L4            10 S L3
L5             3 S L4 AND (RECEPTOR OR CB1 OR CANNABINOID)
L6             0 S L5 AND TREAT?

=> s l5 and activat?
       1046902 ACTIVAT?
L7             1 L5 AND ACTIVAT?

=> dis l7 ibib abs hitstr

L7   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:203609  CAPLUS
DOCUMENT NUMBER:          137:56979
TITLE:                    A structure/activity relationship study on arvanil, an
                          endocannabinoid and vanilloid hybrid
AUTHOR(S):                Di Marzo, Vincenzo; Griffin, Graeme; De Petrocellis,
                          Luciano; Brandi, Ines; Bisogno, Tiziana; Williams,
                          William; Grier, Mark C.; Kulasegram, Sanjitha;
                          Mahadevan, Anu; Razdan, Raj K.; Martin, Billy R.
CORPORATE SOURCE:         Endocannabinoid Research Group, Istituto di Chimica
                          Biomolecolare, Naples, Italy
SOURCE:                   Journal of Pharmacology and Experimental Therapeutics
                          (2002), 300(3), 984-991
                          CODEN: JPETAB; ISSN: 0022-3565
```

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:56979

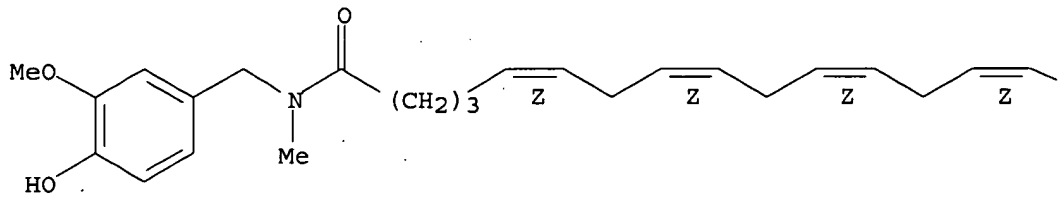
AB Arvanil, a structural "hybrid" between the endogenous **cannabinoid CB1 receptor** ligand anandamide and capsaicin, is a potent agonist for the capsaicin **receptor** VR1 (vanilloid **receptor** type 1), inhibits the anandamide membrane transporter (AMT), and induces cannabimimetic responses in mice. Novel arvanil derivs. prepd. by N-methylation, replacement of the amide with urea and thiourea moieties, and manipulation of the vanillyl group were evaluated for their ability to bind/**activate CB1 receptors**, **activate** VR1 **receptors**, inhibit the AMT and fatty acid amide hydrolase (FAAH), and produce cannabimimetic effects in mice. The compds. did not stimulate the **CB1 receptor**. Methylation of the amide group decreased the activity at VR1, AMT, and FAAH. On the arom. ring, the substitution of the 3-methoxy group with a chlorine atom or the lack of the 4-hydroxy group decreased the activity on VR1 and AMT, but not the affinity for **CB1 receptors**, and increased the capability to inhibit FAAH. The urea or thiourea analogs retained activity at VR1 and AMT but exhibited little affinity for **CB1 receptors**. The urea analog was a potent FAAH inhibitor (IC50 = 2.0 .mu.M). A water-sol. analog of arvanil, O-2142, was as active on VR1, much less active on AMT and **CB1**, and more potent on FAAH. All compds. induced a response in the mouse "tetrad", particularly those with EC50 <10 nM on VR1. However, the most potent compd., N-N'-di-(3-chloro-4-hydroxy)benzyl-arachidonamide (O-2093, ED50 .apprx.0.04 mg/kg), did not **activate** VR1 or **CB1 receptors**. Our findings suggest that VR1 and/or as yet uncharacterized **receptors** produce cannabimimetic responses in mice in vivo.

IT **439079-98-8P**, O 1988
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure/activity relationship study on arvanil)

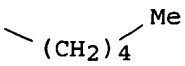
RN 439079-98-8 CAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-N-methyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> file medline
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        29.67     178.83

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                        -2.60      -2.60

FILE 'MEDLINE' ENTERED AT 13:48:57 ON 08 MAY 2003

 FILE LAST UPDATED: 7 MAY 2003 (20030507/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> dis hist

     (FILE 'HOME' ENTERED AT 13:43:09 ON 08 MAY 2003)

     FILE 'REGISTRY' ENTERED AT 13:43:22 ON 08 MAY 2003
L1              STRUCTURE UPLOADED
L2            1 S L1 SSS SAM
L3           11 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:45:01 ON 08 MAY 2003
L4           10 S L3
L5            3 S L4 AND (RECEPTOR OR CB1 OR CANNABINOID)
L6            0 S L5 AND TREAT?
L7            1 S L5 AND ACTIVAT?

     FILE 'MEDLINE' ENTERED AT 13:48:57 ON 08 MAY 2003

=> s l7
             0 L3
        420272 RECEPTOR
        460620 RECEPTORS
        596622 RECEPTOR
                 (RECEPTOR OR RECEPTORS)
           894 CB1
          2594 CANNABINOID
          3073 CANNABINOIDS
          4021 CANNABINOID
                 (CANNABINOID OR CANNABINOIDS)
        606920 ACTIVAT?
L8           0 L5 AND ACTIVAT?

=> file embase
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.98     179.81

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -2.60

FILE 'EMBASE' ENTERED AT 13:50:08 ON 08 MAY 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.
```

```
 FILE COVERS 1974 TO 1 May 2003 (20030501/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l7
            0 L3
       622653 RECEPTOR
       234337 RECEPTORS
       661651 RECEPTOR
                (RECEPTOR OR RECEPTORS)
          885 CB1
         3941 CANNABINOID
         2076 CANNABINOIDS
         4417 CANNABINOID
                (CANNABINOID OR CANNABINOIDS)
       529654 ACTIVAT?
L9           0 L5 AND ACTIVAT?

=> file biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.38     181.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -2.60

FILE 'BIOSIS' ENTERED AT 13:50:29 ON 08 MAY 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC. (R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 7 May 2003 (20030507/ED)


=> s l7
            0 L3
       575810 RECEPTOR
       291946 RECEPTORS
       697766 RECEPTOR
                (RECEPTOR OR RECEPTORS)
         1493 CB1
         3538 CANNABINOID
         2284 CANNABINOIDS
         4637 CANNABINOID
                (CANNABINOID OR CANNABINOIDS)
       625639 ACTIVAT?
L10          0 L5 AND ACTIVAT?

=> dis hist

     (FILE 'HOME' ENTERED AT 13:43:09 ON 08 MAY 2003)

     FILE 'REGISTRY' ENTERED AT 13:43:22 ON 08 MAY 2003
L1              STRUCTURE UPLOADED
L2            1 S L1 SSS SAM
L3           11 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:45:01 ON 08 MAY 2003
```

```
L4            10 S L3
L5             3 S L4 AND (RECEPTOR OR CB1 OR CANNABINOID)
L6             0 S L5 AND TREAT?
L7             1 S L5 AND ACTIVAT?

     FILE 'MEDLINE' ENTERED AT 13:48:57 ON 08 MAY 2003
L8             0 S L7

     FILE 'EMBASE' ENTERED AT 13:50:08 ON 08 MAY 2003
L9             0 S L7

     FILE 'BIOSIS' ENTERED AT 13:50:29 ON 08 MAY 2003
L10            0 S L7

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                  ENTRY    SESSION
FULL ESTIMATED COST                                1.90     183.09

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                  ENTRY    SESSION
CA SUBSCRIBER PRICE                                0.00      -2.60

STN INTERNATIONAL LOGOFF AT 13:51:28 ON 08 MAY 2003


Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssspta1623kxg

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *  Welcome to STN International  * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Jun 03  New e-mail delivery for search results now available
 NEWS  4  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS  5  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS  6  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS  7  Sep 03  JAPIO has been reloaded and enhanced
 NEWS  8  Sep 16  Experimental properties added to the REGISTRY file
 NEWS  9  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 10  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 11  Oct 24  BEILSTEIN adds new search fields
```

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NEWS 12   Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13   Nov 18  DKILIT has been renamed APOLLIT
NEWS 14   Nov 25  More calculated properties added to REGISTRY
NEWS 15   Dec 04  CSA files on STN
NEWS 16   Dec 17  PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17   Dec 17  TOXCENTER enhanced with additional content
NEWS 18   Dec 17  Adis Clinical Trials Insight now available on STN
NEWS 19   Jan 29  Simultaneous left and right truncation added to COMPENDEX,
                  ENERGY, INSPEC
NEWS 20   Feb 13  CANCERLIT is no longer being updated
NEWS 21   Feb 24  METADEX enhancements
NEWS 22   Feb 24  PCTGEN now available on STN
NEWS 23   Feb 24  TEMA now available on STN
NEWS 24   Feb 26  NTIS now allows simultaneous left and right truncation
NEWS 25   Feb 26  PCTFULL now contains images
NEWS 26   Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27   Mar 19  APOLLIT offering free connect time in April 2003
NEWS 28   Mar 20  EVENTLINE will be removed from STN
NEWS 29   Mar 24  PATDPAFULL now available on STN
NEWS 30   Mar 24  Additional information for trade-named substances without
                  structures available in REGISTRY
NEWS 31   Apr 11  Display formats in DGENE enhanced
NEWS 32   Apr 14  MEDLINE Reload
NEWS 33   Apr 17  Polymer searching in REGISTRY enhanced
NEWS 34   Apr 21  Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 35   Apr 21  New current-awareness alert (SDI) frequency in
                  WPIDS/WPINDEX/WPIX
NEWS 36   Apr 28  RDISCLOSURE now available on STN
NEWS 37   May 05  Pharmacokinetic information and systematic chemical names
                  added to PHAR

NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
              MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *



FILE 'HOME' ENTERED AT 13:52:22 ON 08 MAY 2003

=>  reg
REG IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
```

Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:52:51 ON 08 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 6 MAY 2003 HIGHEST RN 511508-58-0
DICTIONARY FILE UPDATES: 6 MAY 2003 HIGHEST RN 511508-58-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

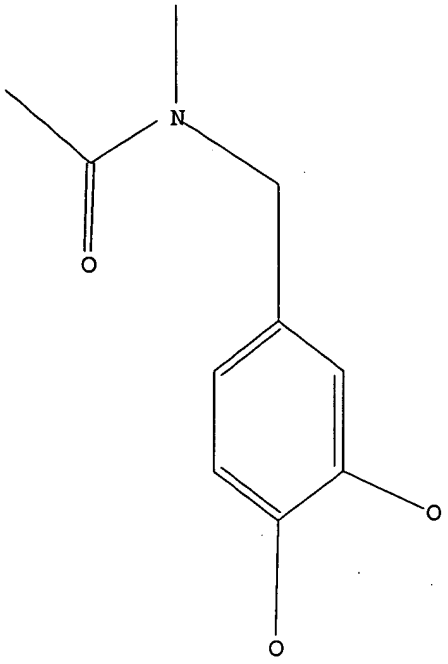
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09787764-1.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> file caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.40	0.61

FILE 'CAPLUS' ENTERED AT 13:53:19 ON 08 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 8 May 2003 VOL 138 ISS 19
FILE LAST UPDATED: 7 May 2003 (20030507/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	1.03

FILE 'REGISTRY' ENTERED AT 13:53:24 ON 08 MAY 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 6 MAY 2003 HIGHEST RN 511508-58-0
DICTIONARY FILE UPDATES: 6 MAY 2003 HIGHEST RN 511508-58-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s l1 sss sam
SAMPLE SEARCH INITIATED 13:53:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 374 TO ITERATE

100.0% PROCESSED 374 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 6320 TO 8640
PROJECTED ANSWERS: 4 TO 200

L2 4 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 13:53:38 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 7813 TO ITERATE

100.0% PROCESSED 7813 ITERATIONS 82 ANSWERS
SEARCH TIME: 00.00.01

L3 82 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY 148.15 TOTAL SESSION 149.18
FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 13:53:47 ON 08 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 8 May 2003 VOL 138 ISS 19
FILE LAST UPDATED: 7 May 2003 (20030507/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3 and vannillinamide
46 L3
0 VANNILLINAMIDE
L4 0 L3 AND VANNILLINAMIDE

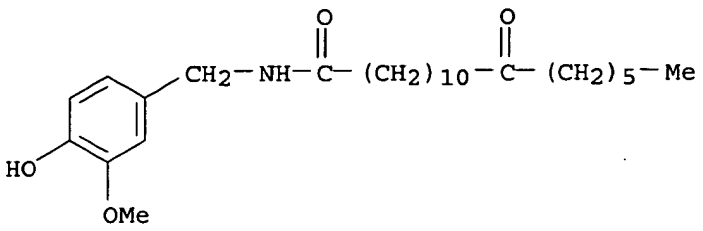
=> s l3 and vanil?
46 L3
19206 VANIL?
L5 2 L3 AND VANIL?

=> dis l5 1-2 ibib abs hitstr

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:511742 CAPLUS
DOCUMENT NUMBER: 137:216814
TITLE: N-Acylvanillamides: Development of an Expeditious Synthesis and Discovery of New Acyl Templates for Powerful Activation of the **Vanilloid** Receptor
AUTHOR(S): Appendino, Giovanni; Minassi, Alberto; Morello, Aniello Schiano; De Petrocellis, Luciano; Di Marzo, Vincenzo
CORPORATE SOURCE: Dipartimento di Scienze Chimiche Alimentari, Farmaceutiche e Farmacologiche, Novara, 28100, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3739-3745
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:216814

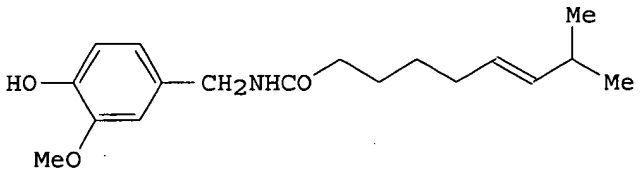
AB A simple and general synthesis of **vanillamides** was developed and employed to screen acids from the fatty and isoprenoid pools for new acyl templates of biol. relevance as capsaicin analogs. Potent activation of the human **vanilloid** receptor 1 (VR1) was obsd. for the **vanillamides** of certain polyfunctional acids from both pools, showing that the **vanilloid** activity of capsaicinoids can be substantially improved by introducing polar groups and/or unsaturations on the acyl moiety. The activity of the unsatd. analogs was maintained or even increased by cyclopropanation, while .omega. dimerization led to a substantial increase of activity. Because of the wide structural diversity of the library of compds. screened, these observations could not be translated into a single framework of structure-activity relationships. Nevertheless, a series of new highly active leads was identified, validating the pharmacol. potential of the unnatural combination of natural building blocks to provide new bioactive compds.

IT **457067-08-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of N-acylvanillamines as templates for **vanilloid** receptor activators)
RN 457067-08-2 CAPLUS
CN Octadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-12-oxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

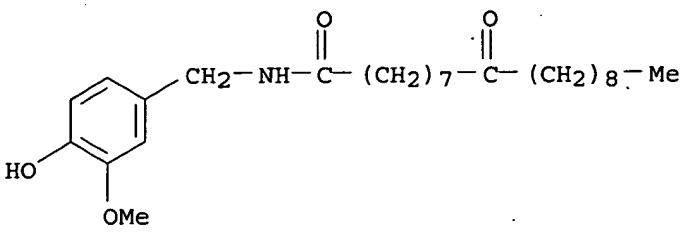
L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:650209 CAPLUS
DOCUMENT NUMBER: 119:250209
TITLE: **Vanilloids**. 1. Analogs of capsaicin with antinociceptive and antiinflammatory activity
AUTHOR(S): Janusz, John M.; Buckwalter, Brian L.; Young, Patricia A.; LaHann, Thomas R.; Farmer, Ralph W.; Kasting, Gerald B.; Loomans, Maurice E.; Kerckaert, Gary A.; Maddin, Cherie S.; et al.
CORPORATE SOURCE: Miami Valley Lab., Procter and Gamble Co., Cincinnati, OH, 45239-8707, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(18), 2595-604
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB As part of a program to establish structure-activity relationships for **vanilloids**, analogs of the pungent principle capsaicin (I), the alkyl chain portion of the parent structure (and related compds. derived from homovanillic acid) was varied. In antinociceptive and antiinflammatory assays (rat and mouse hot plate and croton oil-inflamed mouse ear), compds. with widely varying alkyl chain structures were active. Short-chain compds. were active by systemic administration in the assay mentioned above but they retained the high pungency and acute toxicity characteristic of capsaicin. In contrast, the long chain cis-unsaturates, NE-19550 (**vanillyloleamide**) and NE-28345 (oleylhomovanillamide), were orally active, less pungent, and less acutely toxic than capsaicin. The potential of these compds. as antiinflammatory/analgesic agents is discussed in light of recent data on the mechanism of action of **vanilloids** on sensory nerve fibers.

IT **150988-84-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and antinociceptive and antiinflammatory activity of)
RN 150988-84-4 CAPLUS
CN Octadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-9-oxo- (9CI) (CA INDEX NAME)



```
=> dis hist

     (FILE 'HOME' ENTERED AT 13:52:22 ON 08 MAY 2003)

     FILE 'REGISTRY' ENTERED AT 13:52:51 ON 08 MAY 2003
L1              STRUCTURE UPLOADED

     FILE 'CAPLUS' ENTERED AT 13:53:19 ON 08 MAY 2003

     FILE 'REGISTRY' ENTERED AT 13:53:24 ON 08 MAY 2003
L2            4 S L1 SSS SAM
L3           82 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:53:47 ON 08 MAY 2003
L4            0 S L3 AND VANNILLINAMIDE
L5            2 S L3 AND VANIL?

=> s l3 and receptor
            46 L3
        510540 RECEPTOR
        466647 RECEPTORS
        608028 RECEPTOR
                 (RECEPTOR OR RECEPTORS)
L6            3 L3 AND RECEPTOR

=> s l6 and (cannabinoid or CB1)
          4164 CANNABINOID
          3479 CANNABINOIDS
          4912 CANNABINOID
                 (CANNABINOID OR CANNABINOIDS)
          1547 CB1
L7            0 L6 AND (CANNABINOID OR CB1)

=> dis l6 1-3 bib abs hitstr

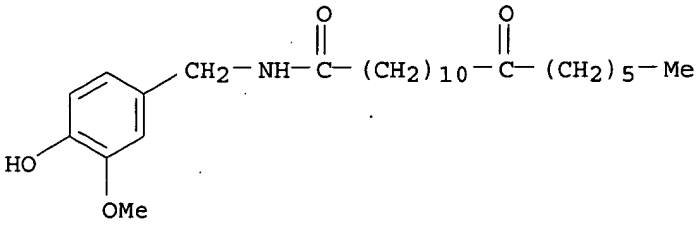
L6   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:511742  CAPLUS
DN   137:216814
TI   N-Acylvanillamides: Development of an Expeditious Synthesis and Discovery
     of New Acyl Templates for Powerful Activation of the Vanilloid
     Receptor
AU   Appendino, Giovanni; Minassi, Alberto; Morello, Aniello Schiano; De
     Petrocellis, Luciano; Di Marzo, Vincenzo
CS   Dipartimento di Scienze Chimiche Alimentari, Farmaceutiche e
     Farmacologiche, Novara, 28100, Italy
SO   Journal of Medicinal Chemistry (2002), 45(17), 3739-3745
     CODEN: JMCMAR; ISSN: 0022-2623
PB   American Chemical Society
DT   Journal
LA   English
OS   CASREACT 137:216814
AB   A simple and general synthesis of vanillamides was developed and employed
```

to screen acids from the fatty and isoprenoid pools for new acyl templates of biol. relevance as capsaicin analogs. Potent activation of the human vanilloid **receptor** 1 (VR1) was obsd. for the vanillamides of certain polyfunctional acids from both pools, showing that the vanilloid activity of capsaicinoids can be substantially improved by introducing polar groups and/or unsaturations on the acyl moiety. The activity of the unsatd. analogs was maintained or even increased by cyclopropanation, while .omega. dimerization led to a substantial increase of activity. Because of the wide structural diversity of the library of compds. screened, these observations could not be translated into a single framework of structure-activity relationships. Nevertheless, a series of new highly active leads was identified, validating the pharmacol. potential of the unnatural combination of natural building blocks to provide new bioactive compds.

IT **457067-08-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of N-acylvanillamines as templates for vanilloid **receptor** activators)

RN 457067-08-2 CAPLUS

CN Octadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-12-oxo- (9CI) (CA INDEX NAME)



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2001:380438 CAPLUS
DN 135:24657
TI Selective cellular targeting: multifunctional delivery vehicles
IN Glazier, Arnold
PA Drug Innovation + Design, Inc., USA
SO PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001016075	A5	20010530	AU 2001-16075	20001114
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI US 1999-165485P	P	19991115		

US 2000-239478P P 20001011
US 2000-241937P P 20001020
WO 2000-US31262 W 20001114

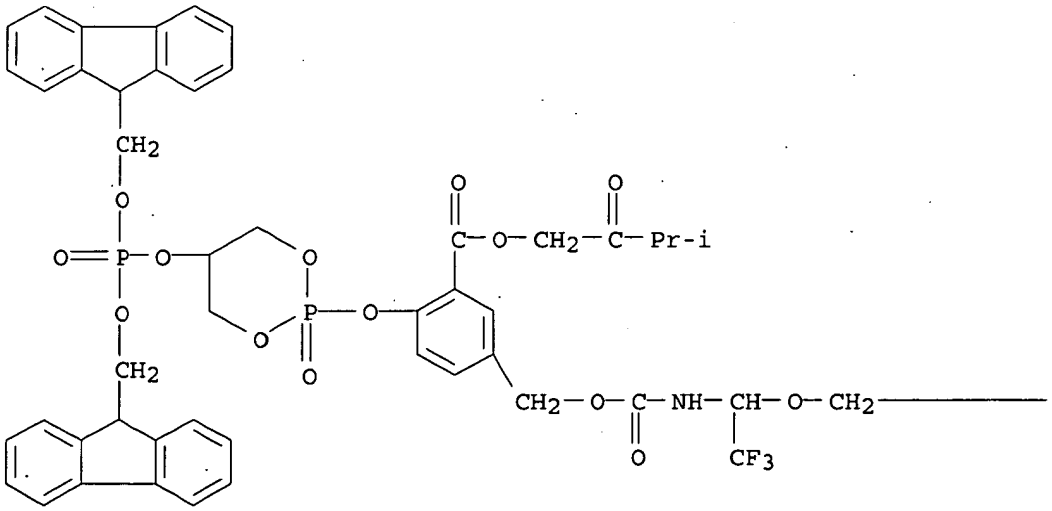
AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

IT **341553-26-2P 341553-32-0P 341553-33-1P**
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341553-26-2 CAPLUS

CN 1H-1,4-Diazepinium, 1-[3-[[4-[2-(2-aminoethoxy)ethoxy]-3,5-dimethoxybenzoyl]amino]propyl]-1-[[1-[[[[4-[[5-[[bis(9H-fluoren-9-ylmethoxy)phosphinyl]oxy]-2-oxido-1,3,2-dioxaphosphorinan-2-yl]oxy]-3-[(3-methyl-2-oxobutoxy)carbonyl]phenyl]methoxy]carbonyl]amino]-2,2,2-trifluoroethoxy]methyl]hexahydro-4-[4-[(3,4,5-trimethoxybenzoyl)amino]butyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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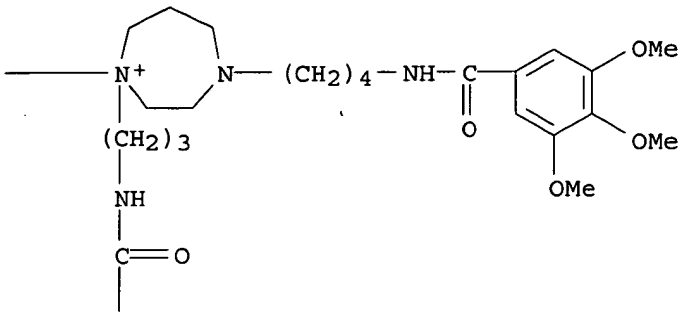

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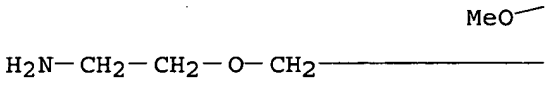

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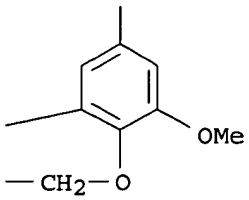

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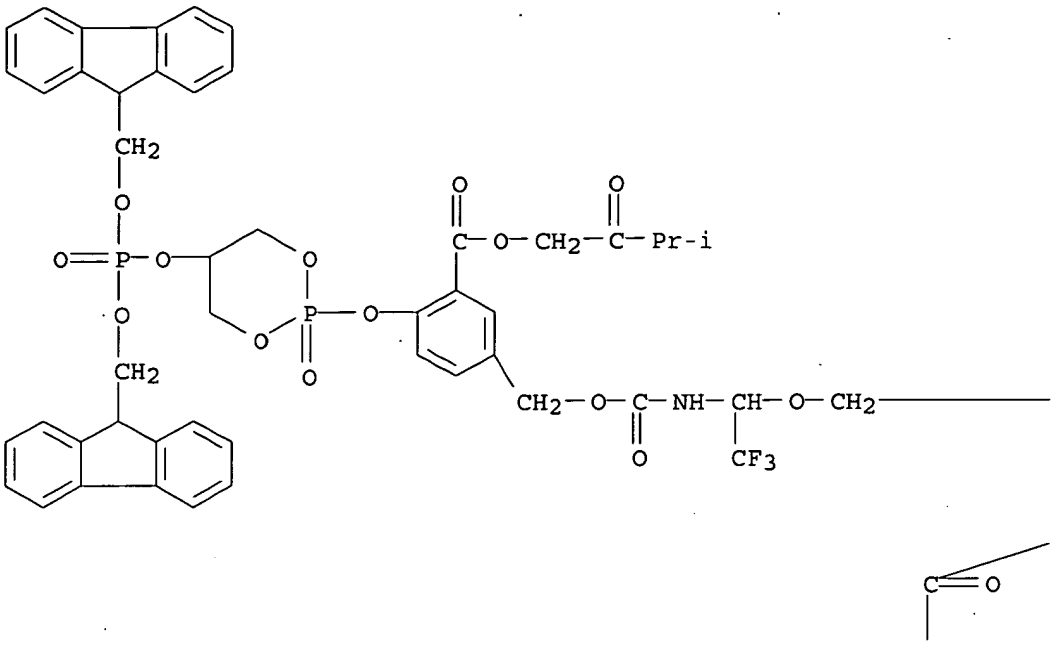
PAGE 1-A



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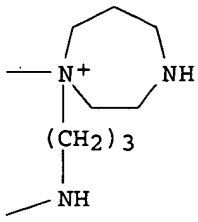

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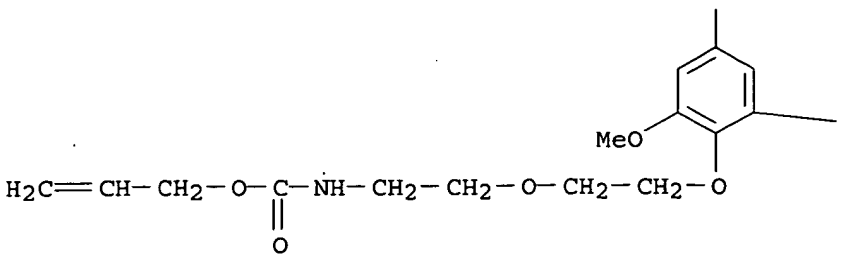

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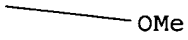

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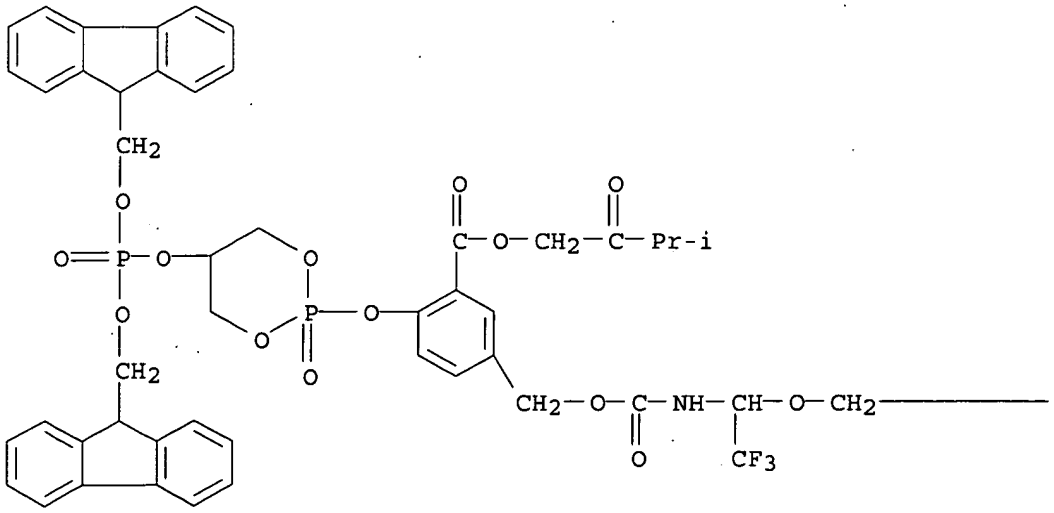
PAGE 1-A



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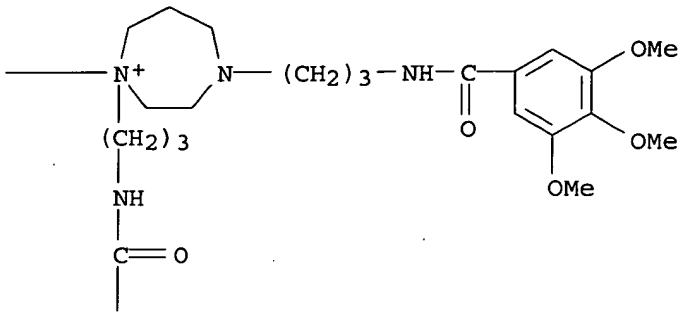

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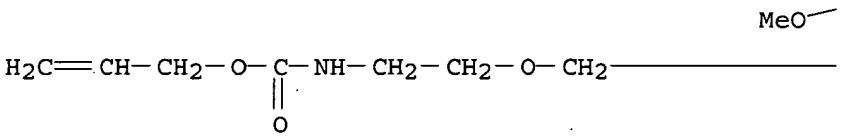

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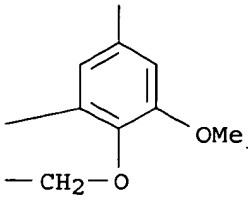


L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 1998:617887 CAPLUS
DN 129:330462
TI Higher order iminodiacetic acid libraries for probing protein-protein interactions
AU Boger, Dale L.; Goldberg, Joel; Jiang, Weiqin; Chai, Wenying; Ducray, Pierre; Lee, Jae Kyoo; Ozer, Rachel S.; Andersson, Carl-Magnus
CS Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (1998), 6(8), 1347-1378

CODEN: BMECEP; ISSN: 0968-0896

PB Elsevier Science Ltd.

DT Journal

LA English

AB Full details of the prepn. of iminodiacetic acid diamide dimer (2040 compds.), trimer (560 compds.), and tetramer (1596 compds.) libraries by multistep convergent soln.-phase synthesis for studying protein-protein interactions are provided. The libraries were assembled in a format providing small 8-10 compd. mixts. and the deconvolution of many of the small mixts. to identify screening leads by resynthesis of the individual components were conducted for 320 of the individual compds. to date. A representative example of the subsequent exploration of the structure-activity relationships for an identified **receptor** binding antagonist (200 addnl. individual compds.) and steps taken for potential elaboration to a **receptor** dimerization agonist are defined with prepn. of representative linked dimers (70 compds.).

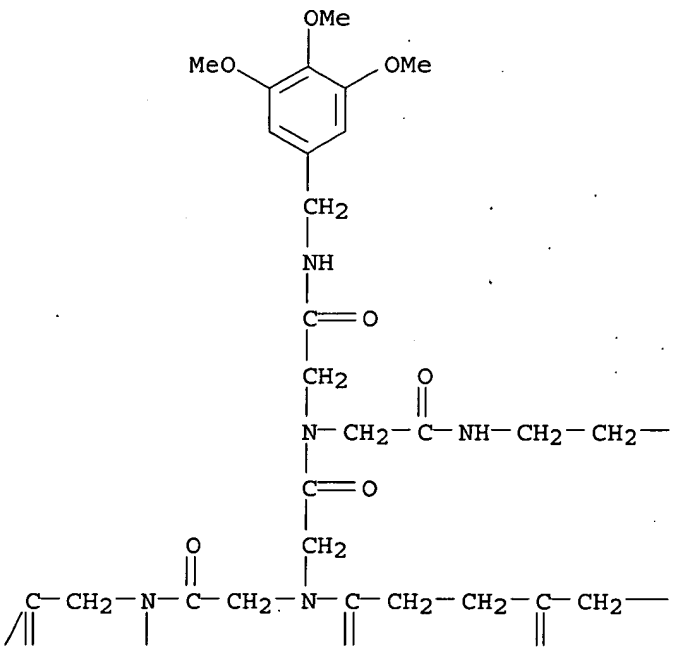
IT **215161-53-8P 215161-54-9P**

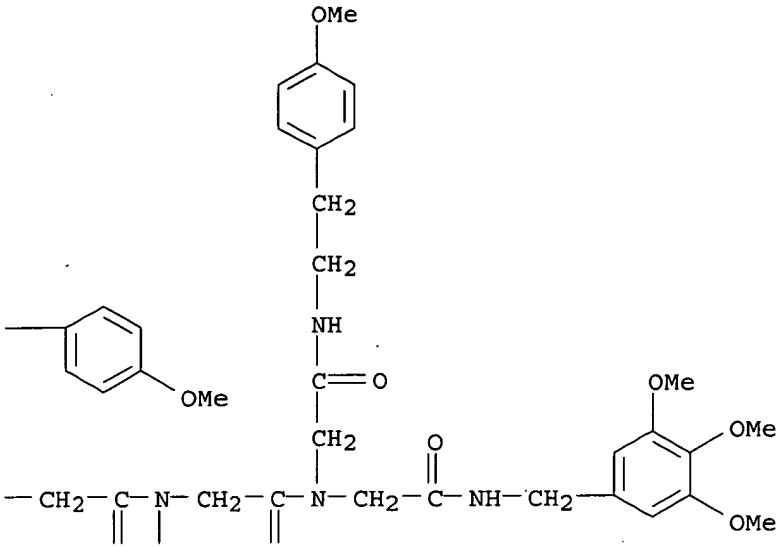
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of higher order iminodiacetic acid libraries for probing protein-protein interactions)

RN 215161-53-8 CAPLUS

CN Glycinamide, 1,1'-(1,4,7-trioxo-1,7-heptanediyl)bis[N-[2-[[2-[[2-(4-methoxyphenyl)ethyl]amino]-2-oxoethyl][2-oxo-2-[[(3,4,5-trimethoxyphenyl)methyl]amino]ethyl]amino]-2-oxoethyl]glycyl-N2-[2-[[2-(4-methoxyphenyl)ethyl]amino]-2-oxoethyl]-N-[(3,4,5-trimethoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

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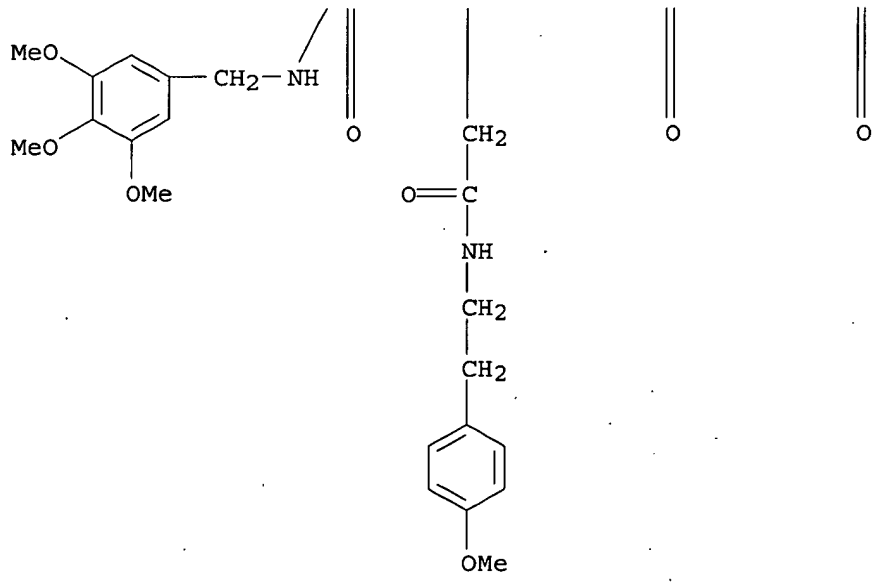
NH
C=O
OMe
CH2
O
OMe
OMe
OMe
CH2 C N CH2 C N CH2 C NH CH2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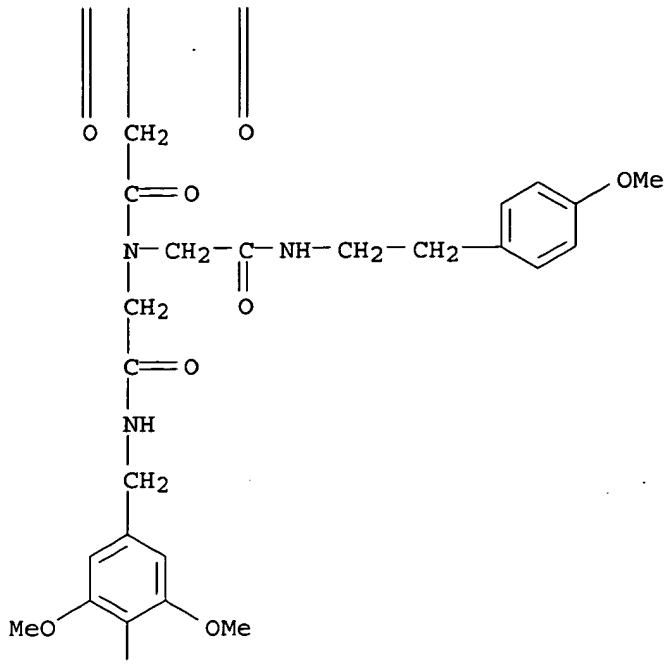
PAGE 2-B



PAGE 3-B

RN 215161-54-9 CAPLUS
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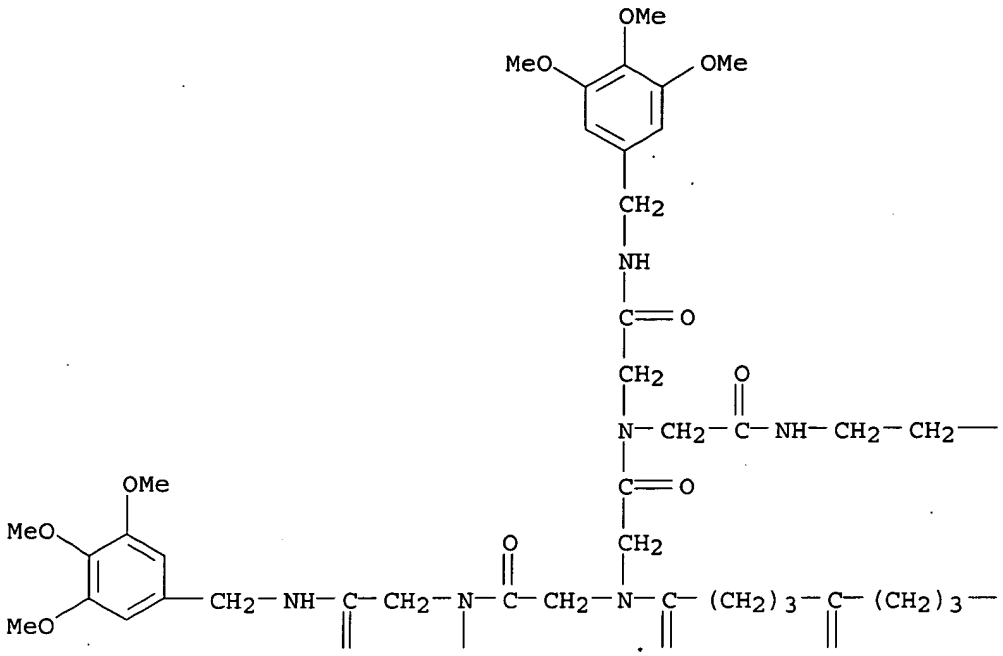
PAGE 1-A



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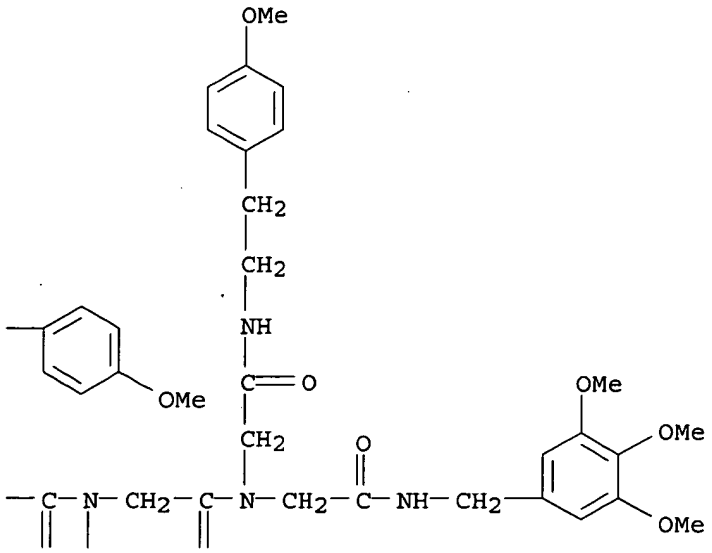

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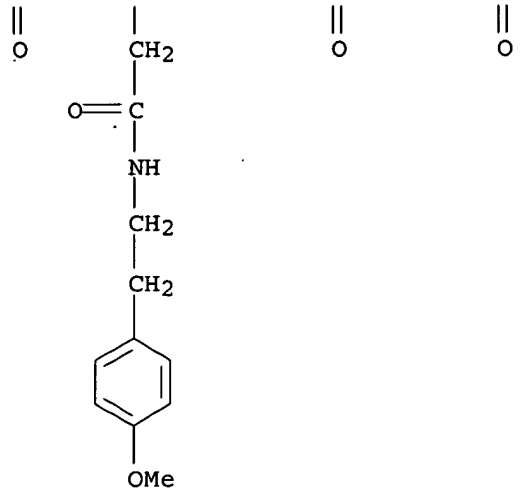
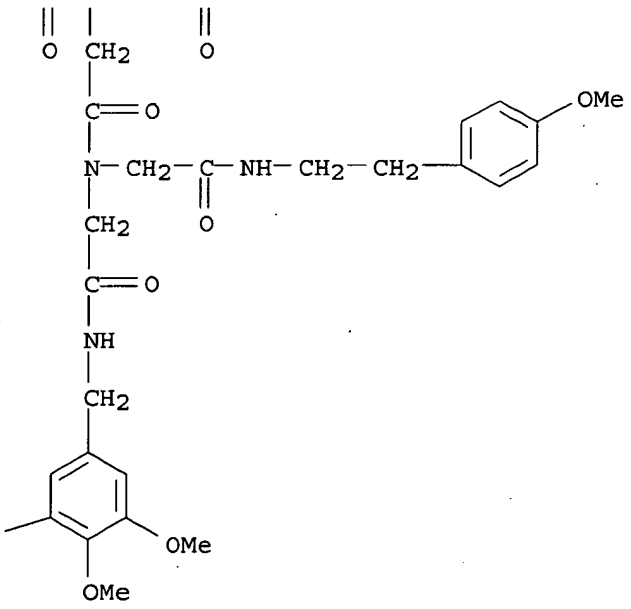


PAGE 2-B



RE.CNT 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 13:52:51 ON 08 MAY 2003
L1 STRUCTURE UPLOADED

FILE 'CAPLUS' ENTERED AT 13:53:19 ON 08 MAY 2003

FILE 'REGISTRY' ENTERED AT 13:53:24 ON 08 MAY 2003
L2 4 S L1 SSS SAM

```
L3            82 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:53:47 ON 08 MAY 2003
L4             0 S L3 AND VANNILLINAMIDE
L5             2 S L3 AND VANIL?
L6             3 S L3 AND RECEPTOR
L7             0 S L6 AND (CANNABINOID OR CB1)

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    37.13     186.31

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.26      -3.26

FILE 'MEDLINE' ENTERED AT 14:02:00 ON 08 MAY 2003

 FILE LAST UPDATED: 7 MAY 2003 (20030507/UP). FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l6
             0 L3
        420272 RECEPTOR
        460620 RECEPTORS
        596622 RECEPTOR
                 (RECEPTOR OR RECEPTORS)
L8           0 L3 AND RECEPTOR

=> file embase
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     2.02     188.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -3.26

FILE 'EMBASE' ENTERED AT 14:02:20 ON 08 MAY 2003
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 FILE COVERS 1974 TO 1 May 2003 (20030501/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l6
             0 L3
        622653 RECEPTOR
        234337 RECEPTORS
        661651 RECEPTOR
                 (RECEPTOR OR RECEPTORS)
L9           0 L3 AND RECEPTOR
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=> file biosis
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         2.80     191.13

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -3.26

FILE 'BIOSIS' ENTERED AT 14:02:37 ON 08 MAY 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 7 May 2003 (20030507/ED)


=> s l6
             0 L3
        575810 RECEPTOR
        291946 RECEPTORS
        697766 RECEPTOR
                  (RECEPTOR OR RECEPTORS)
L10          0 L3 AND RECEPTOR

=> d scan
L10 HAS NO ANSWERS


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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         5.84     196.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -3.26

FILE 'REGISTRY' ENTERED AT 14:05:24 ON 08 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    6 MAY 2003  HIGHEST RN 511508-58-0
DICTIONARY FILE UPDATES:   6 MAY 2003  HIGHEST RN 511508-58-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d scan
L10 HAS NO ANSWERS
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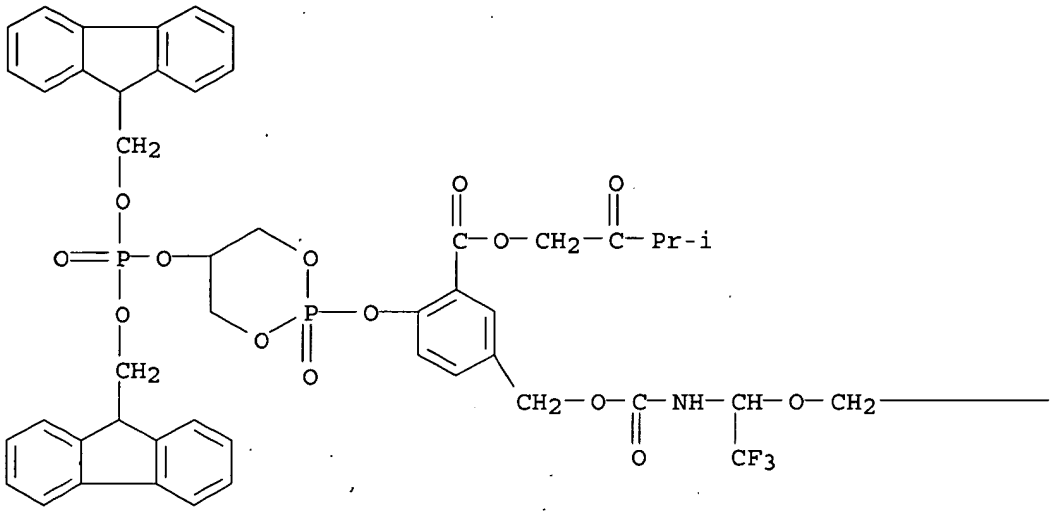
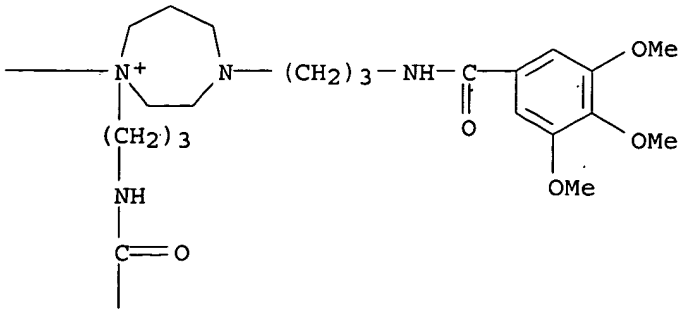
=> d scan l3

L3 82 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-1,4-Diazepinium, 1-[[1-[[[[4-[[5-[[bis(9H-fluoren-9-ylmethoxy)phosphinyl]oxy]-2-oxido-1,3,2-dioxaphosphorinan-2-yl]oxy]-3-[(3-methyl-2-oxobutoxy)carbonyl]phenyl]methoxy]carbonyl]amino]-2,2,2-trifluoroethoxy]methyl]-1-[3-[[3,5-dimethoxy-4-[2-[2-[[(2-propenyloxy)carbonyl]amino]ethoxy]ethoxy]benzoyl]amino]propyl]hexahydro-4-[3-[(3,4,5-trimethoxybenzoyl)amino]propyl]- (9CI)
MF C86 H102 F3 N6 O25 P2

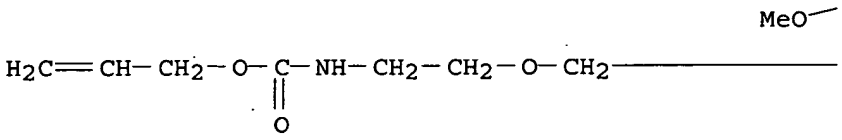
PAGE 1-A



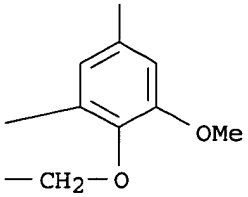
PAGE 1-B



PAGE 2-A



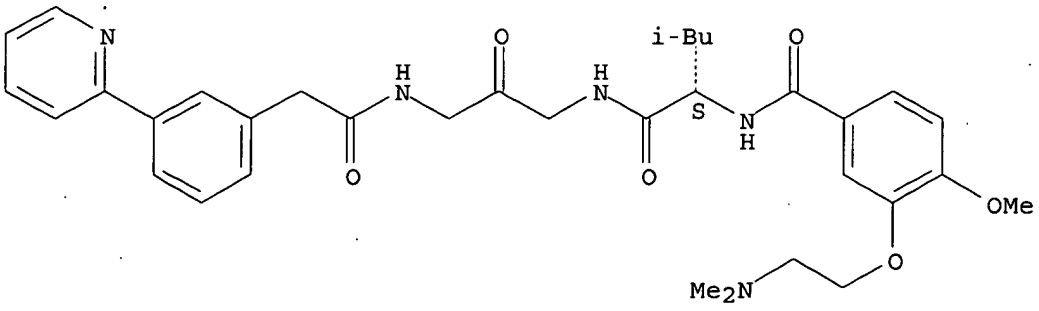
PAGE 2-B



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 82 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzeneacetamide, N-[3-[[(2S)-2-[[3-[2-(dimethylamino)ethoxy]-4-methoxybenzoyl]amino]-4-methyl-1-oxopentyl]amino]-2-oxopropyl]-3-(2-pyridinyl)- (9CI)
MF C34 H43 N5 O6

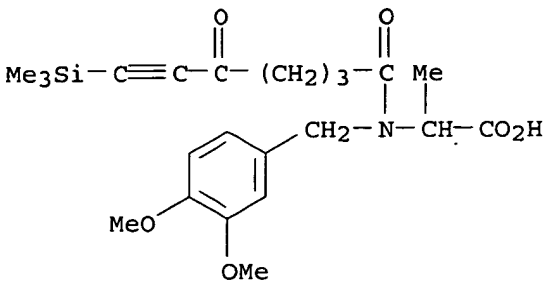
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

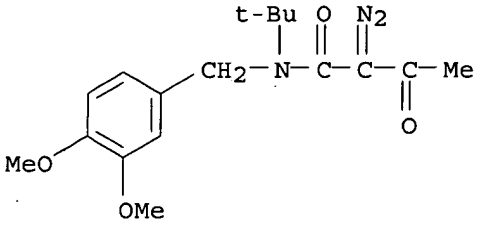
L3 82 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Alanine, N-[(3,4-dimethoxyphenyl)methyl]-N-[1,5-dioxo-7-(trimethylsilyl)-6-heptynyl]- (9CI)
MF C22 H31 N O6 Si



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

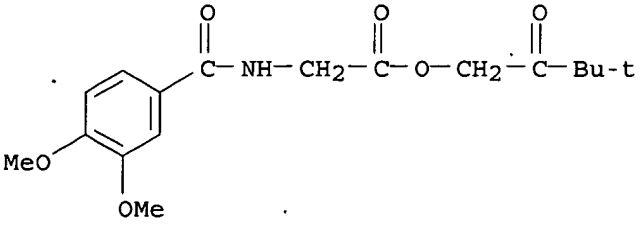
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 82 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Butanamide, 2-diazo-N-[(3,4-dimethoxyphenyl)methyl]-N-(1,1-dimethylethyl)-3-oxo- (9CI)
MF C17 H23 N3 O4



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 82 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Glycine, N-(3,4-dimethoxybenzoyl)-, 3,3-dimethyl-2-oxobutyl ester (9CI)
MF C17 H23 N O6



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

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FILE 'REGISTRY' ENTERED AT 13:52:51 ON 08 MAY 2003
L1 STRUCTURE UPLOADED

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     FILE 'REGISTRY' ENTERED AT 13:53:24 ON 08 MAY 2003
L2             4 S L1 SSS SAM
L3            82 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:53:47 ON 08 MAY 2003
L4             0 S L3 AND VANNILLINAMIDE
L5             2 S L3 AND VANIL?
L6             3 S L3 AND RECEPTOR
L7             0 S L6 AND (CANNABINOID OR CB1)

     FILE 'MEDLINE' ENTERED AT 14:02:00 ON 08 MAY 2003
L8             0 S L6

     FILE 'EMBASE' ENTERED AT 14:02:20 ON 08 MAY 2003
L9             0 S L6

     FILE 'BIOSIS' ENTERED AT 14:02:37 ON 08 MAY 2003
L10            0 S L6

     FILE 'REGISTRY' ENTERED AT 14:05:24 ON 08 MAY 2003

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               1.20     198.17

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                               0.00      -3.26

STN INTERNATIONAL LOGOFF AT 14:06:59 ON 08 MAY 2003
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L3           11 S L1 SSS FULL

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L4           10 S L3
L5            3 S L4 AND (RECEPTOR OR CB1 OR CANNABINOID)
L6            0 S L5 AND TREAT?
L7            1 S L5 AND ACTIVAT?

     FILE 'MEDLINE' ENTERED AT 13:48:57 ON 08 MAY 2003
L8            0 S L7

     FILE 'EMBASE' ENTERED AT 13:50:08 ON 08 MAY 2003
L9            0 S L7

     FILE 'BIOSIS' ENTERED AT 13:50:29 ON 08 MAY 2003
L10           0 S L7
```

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=> dis hist

     (FILE 'HOME' ENTERED AT 13:52:22 ON 08 MAY 2003)

     FILE 'REGISTRY' ENTERED AT 13:52:51 ON 08 MAY 2003
L1             STRUCTURE UPLOADED

     FILE 'CAPLUS' ENTERED AT 13:53:19 ON 08 MAY 2003

     FILE 'REGISTRY' ENTERED AT 13:53:24 ON 08 MAY 2003
L2             4 S L1 SSS SAM
L3            82 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:53:47 ON 08 MAY 2003
L4             0 S L3 AND VANNILLINAMIDE
L5             2 S L3 AND VANIL?
L6             3 S L3 AND RECEPTOR
L7             0 S L6 AND (CANNABINOID OR CB1)

     FILE 'MEDLINE' ENTERED AT 14:02:00 ON 08 MAY 2003
L8             0 S L6

     FILE 'EMBASE' ENTERED AT 14:02:20 ON 08 MAY 2003
L9             0 S L6

     FILE 'BIOSIS' ENTERED AT 14:02:37 ON 08 MAY 2003
L10            0 S L6

     FILE 'REGISTRY' ENTERED AT 14:05:24 ON 08 MAY 2003
```